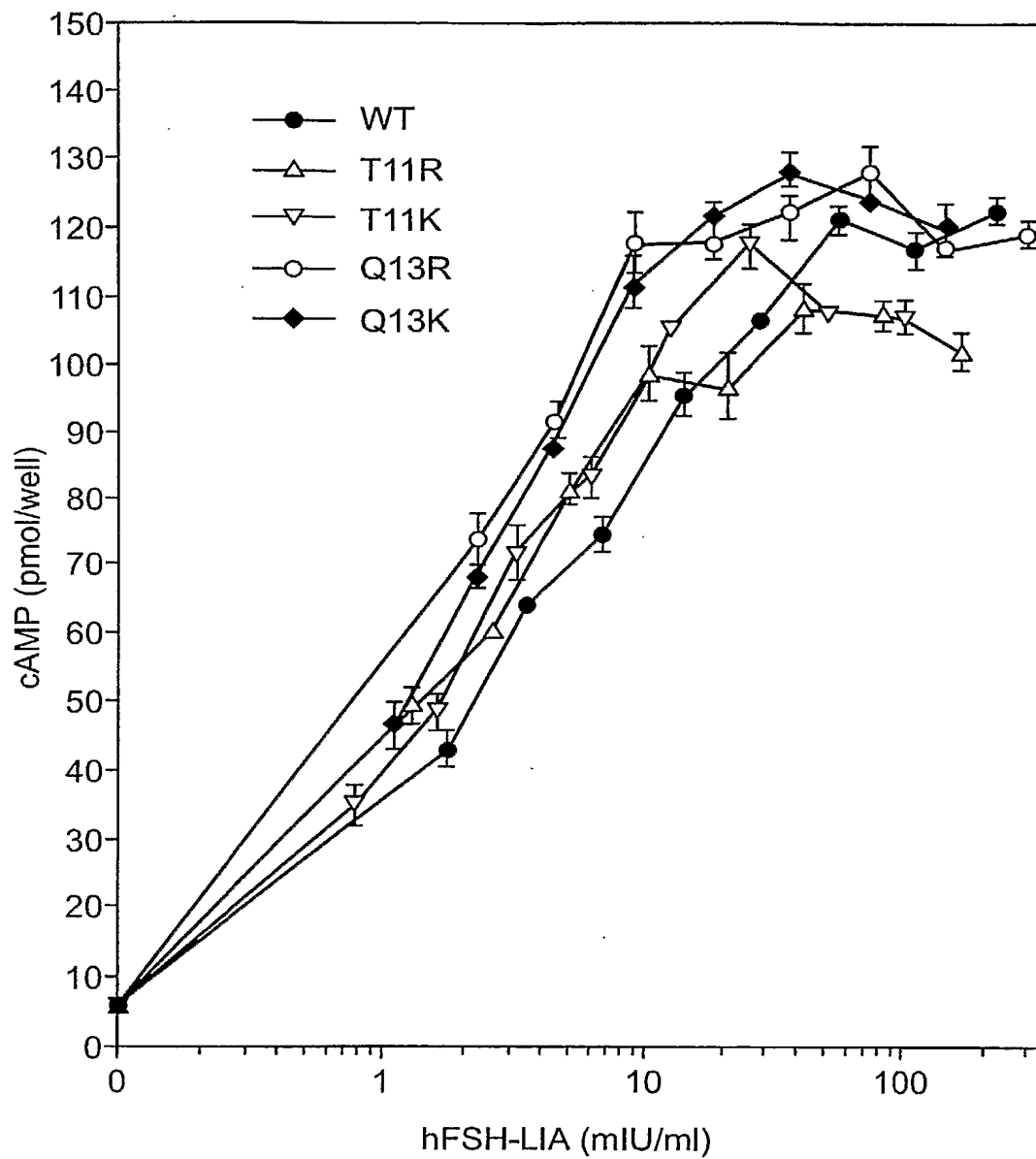


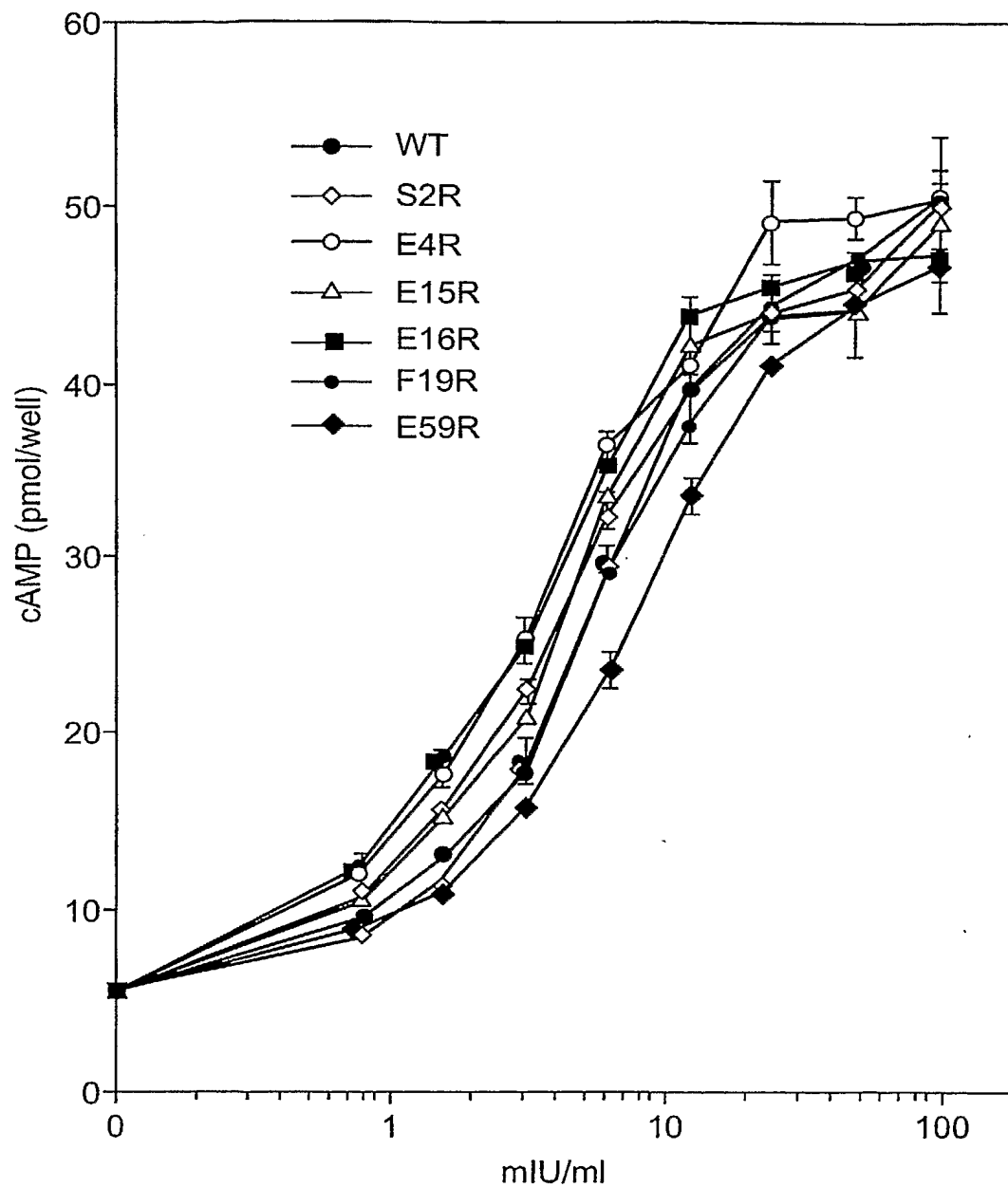
1/37

EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO
STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS

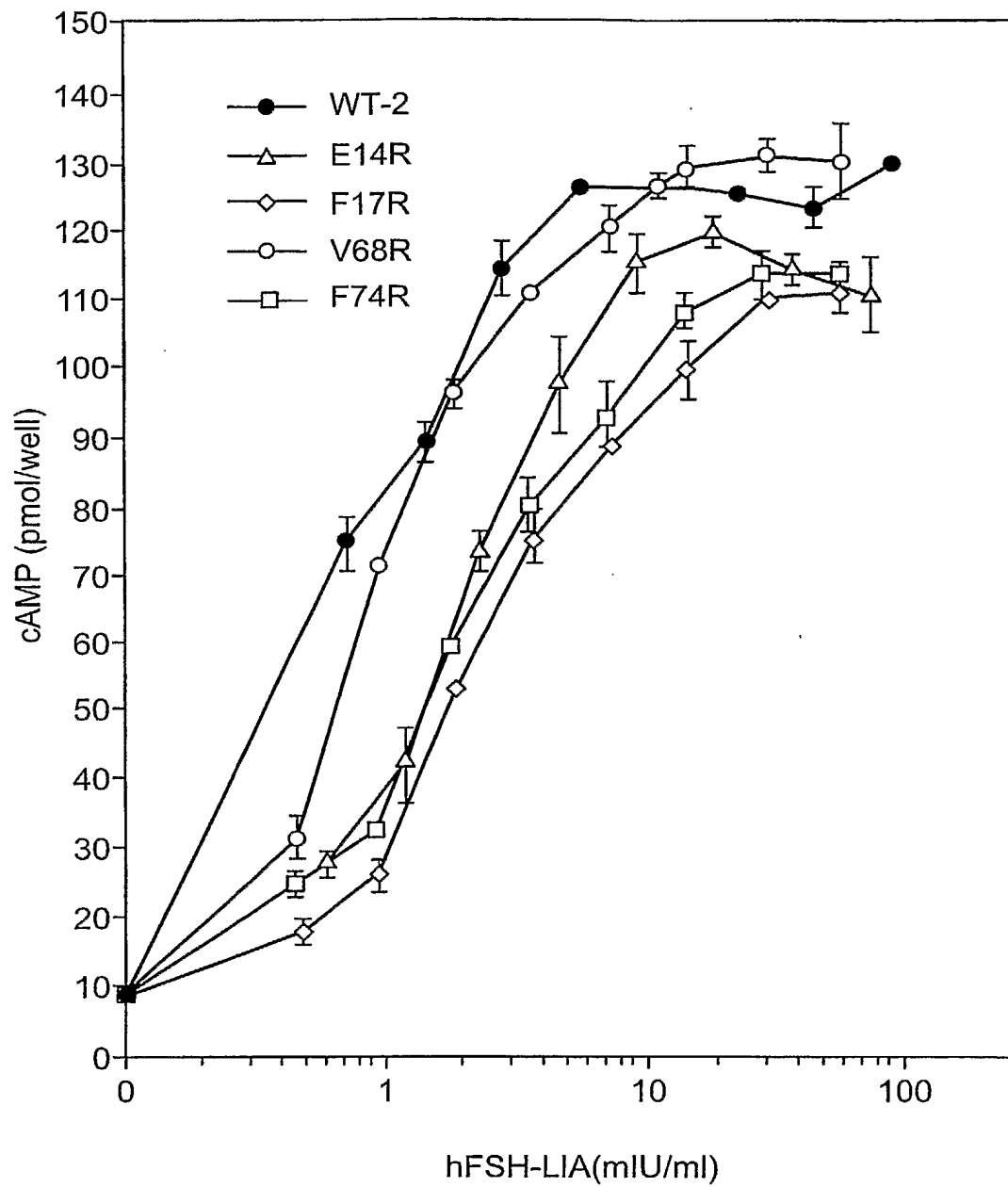
**FIG. 1A**

2/37

EFFECT OF SINGLE MUTATIONS ON FSH BIOACTIVITY IN VITRO

**FIG. 1B**

3/37

STIMULATION OF cAMP PRODUCTION
IN CHO-FSHR CELLS**FIG. 1C**

4/37

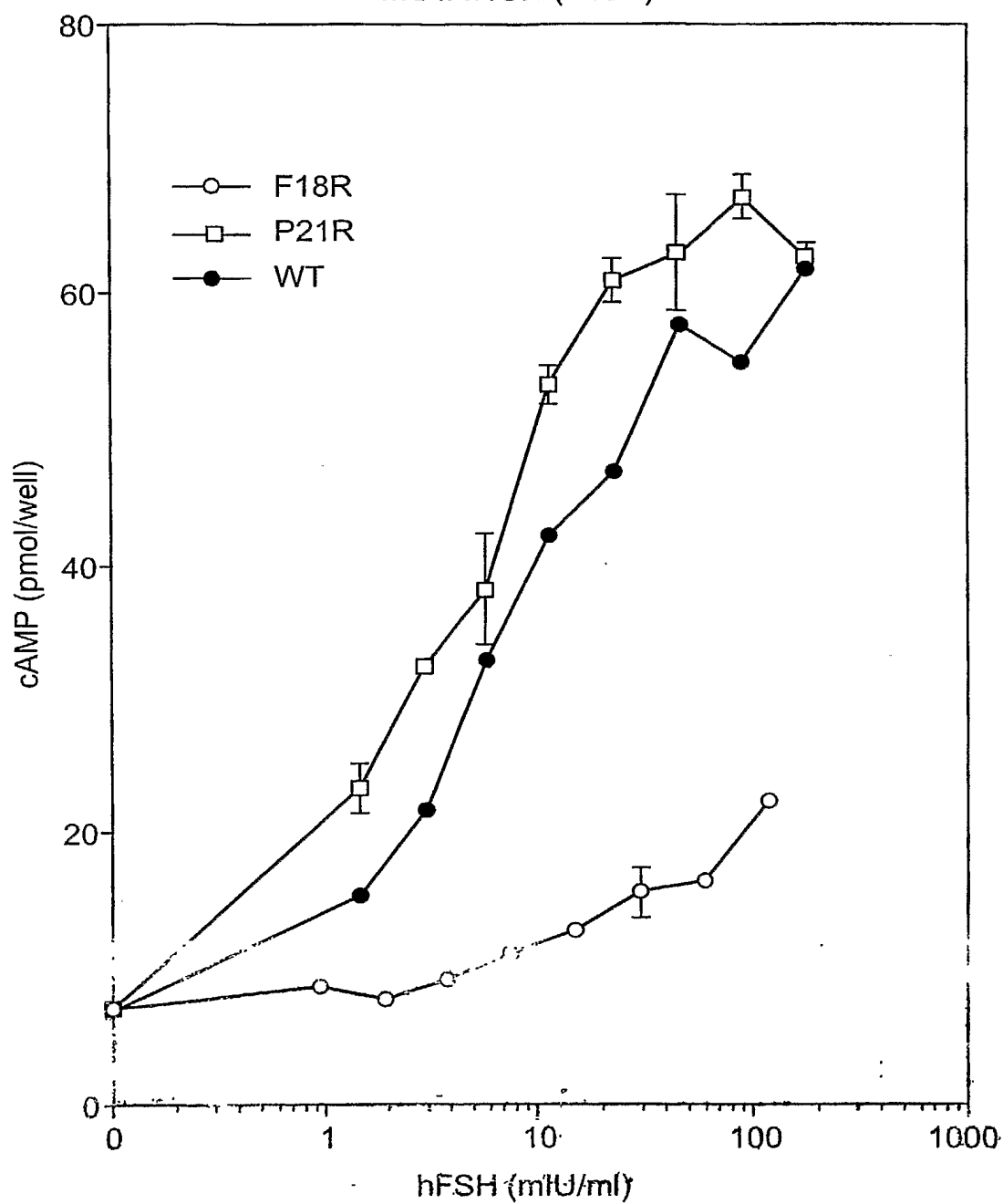
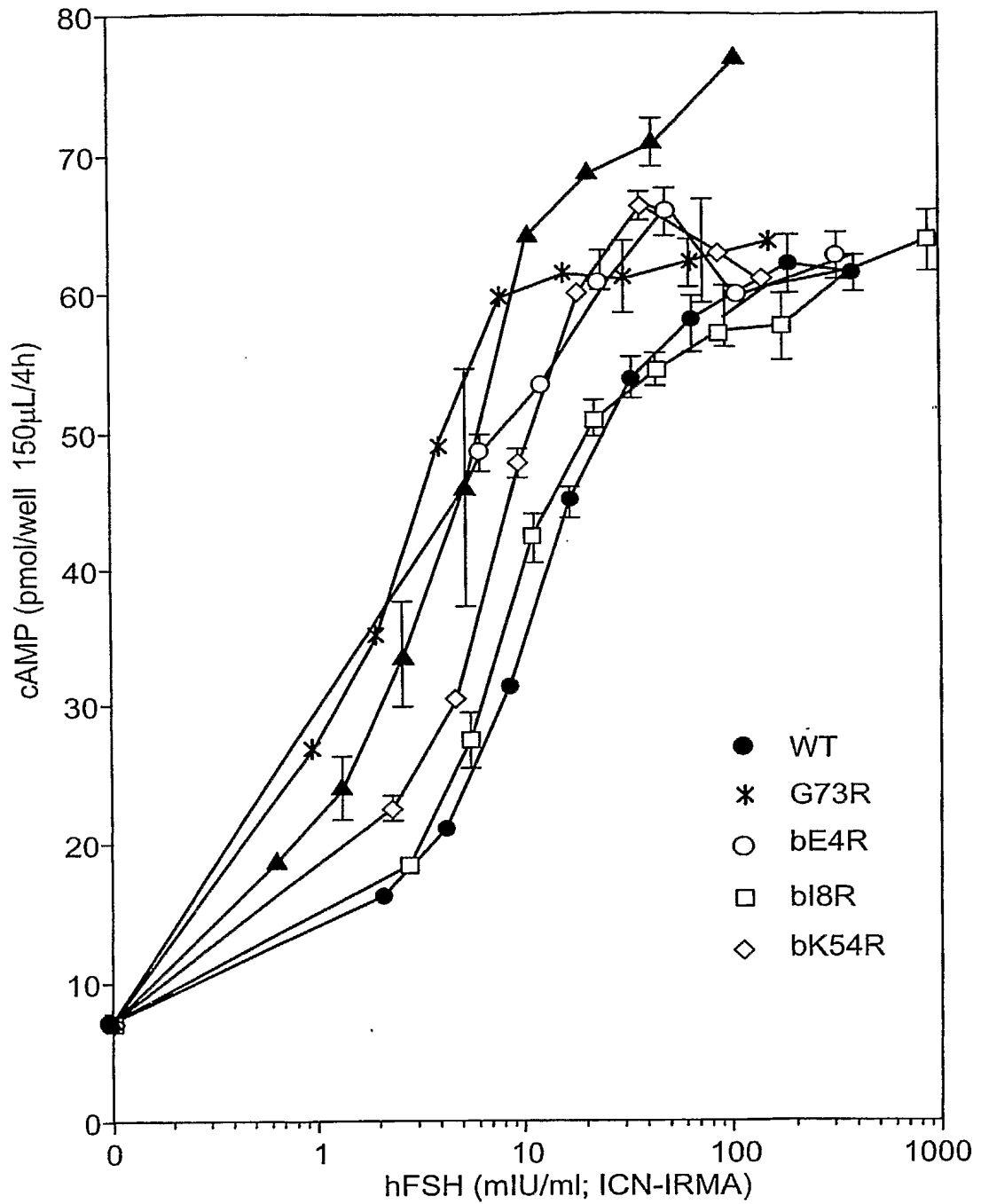
EXAMPLE OF "LOSS OF BIOACTIVITY"
MUTATION (F18R)

FIG. 1D

5/37

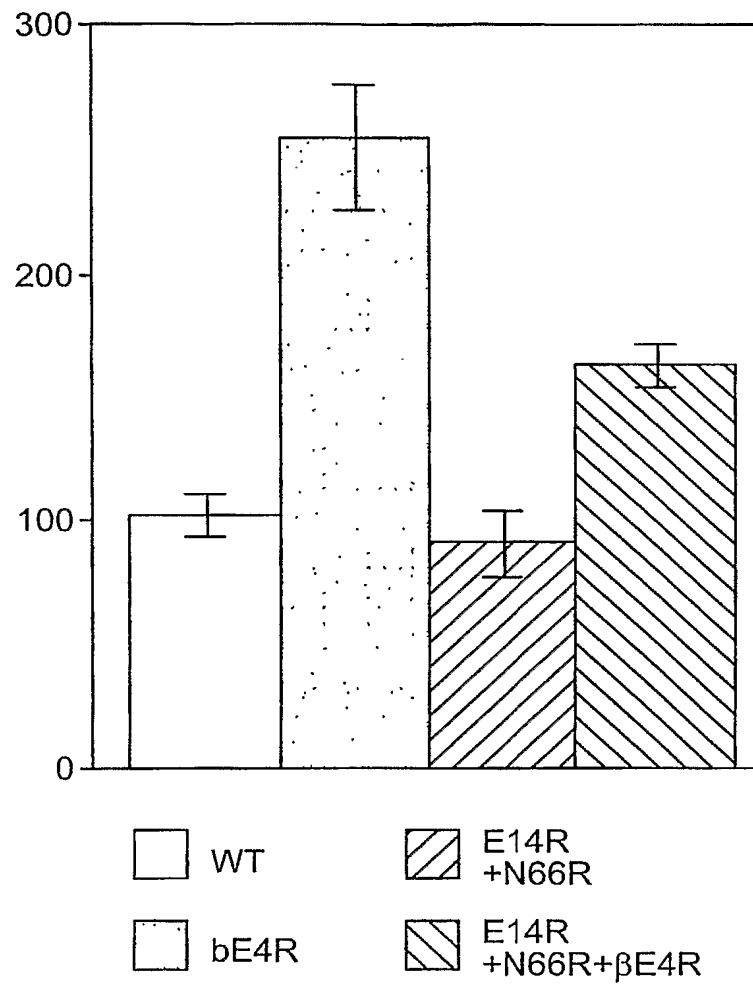
cAMP STIMULATION IN CHO-FSHR CELLS

**FIG. 1E**

6/37

EFFECT OF β E4R MUTATION ON hFSH PRODUCTION

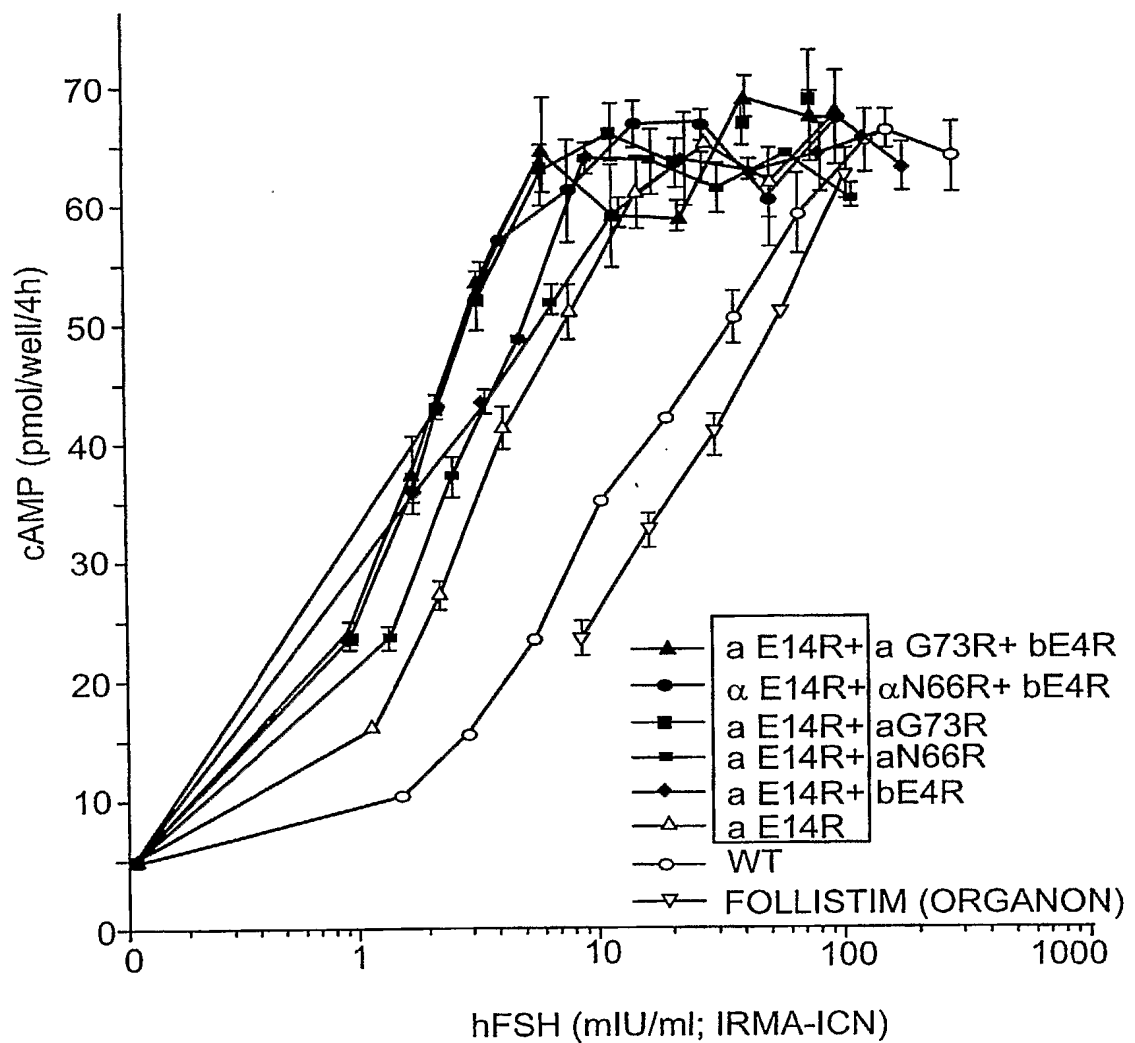
%WT
(PRODUCTION
OF NON-
MUTATED
FSH=100%)

**FIG. 2**

7/37

FSH ANALOGS WITH COMBINED SUBSTITUTIONS

cAMP STIMULATION IN CHO-FSHR CELLS

**FIG. 3A**

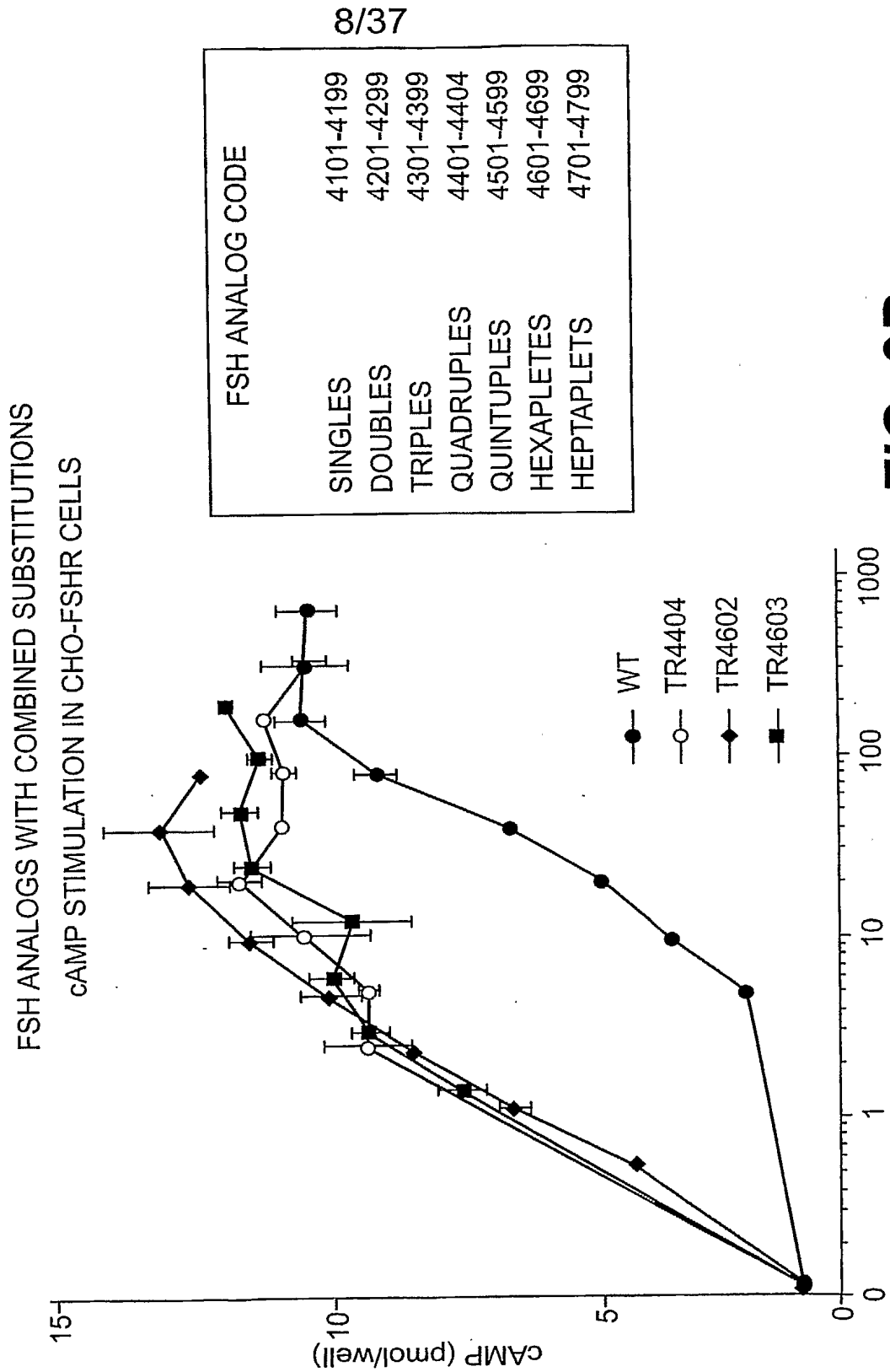
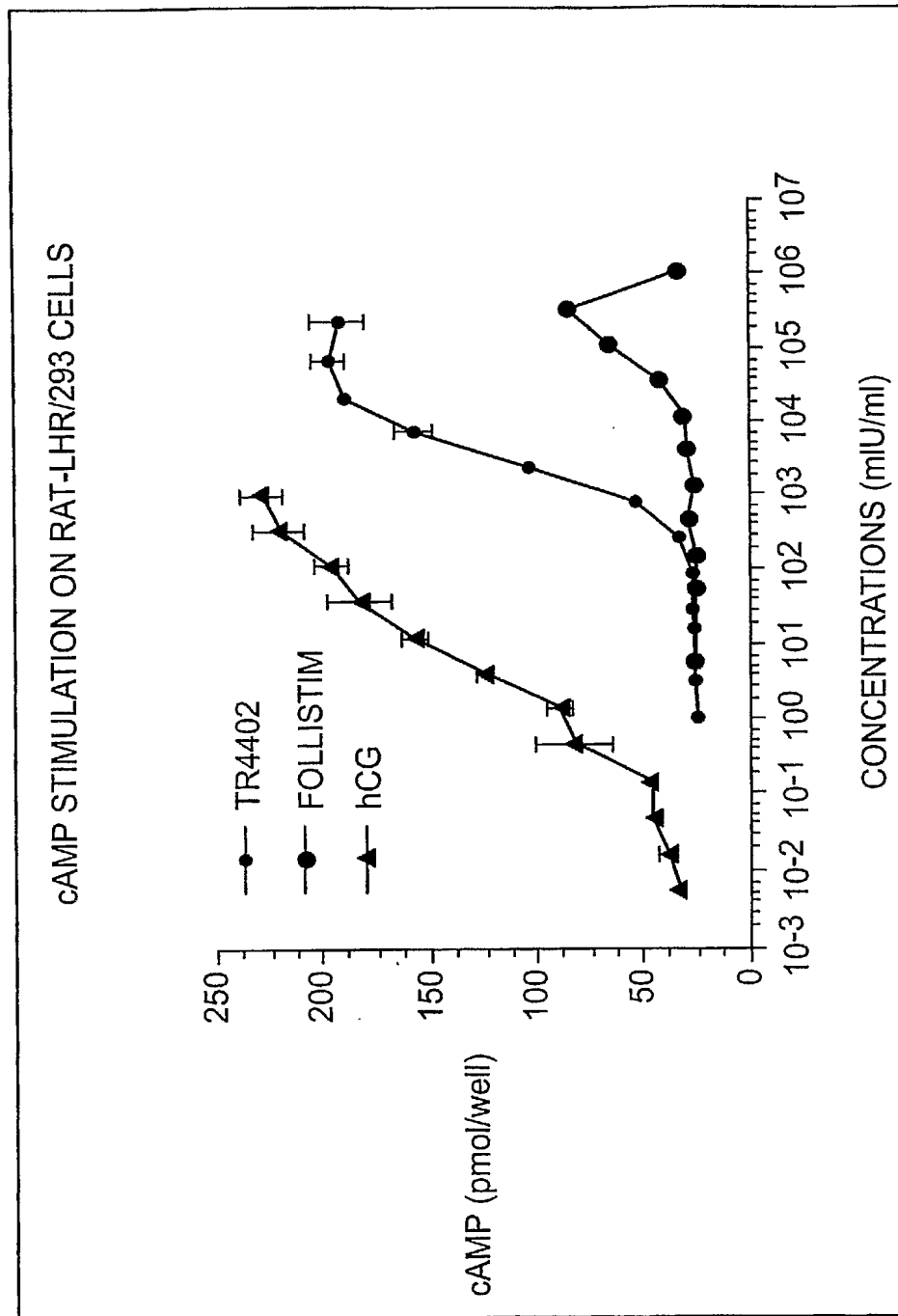


FIG. 3B

9/37

**FIG. 4A**

10/37

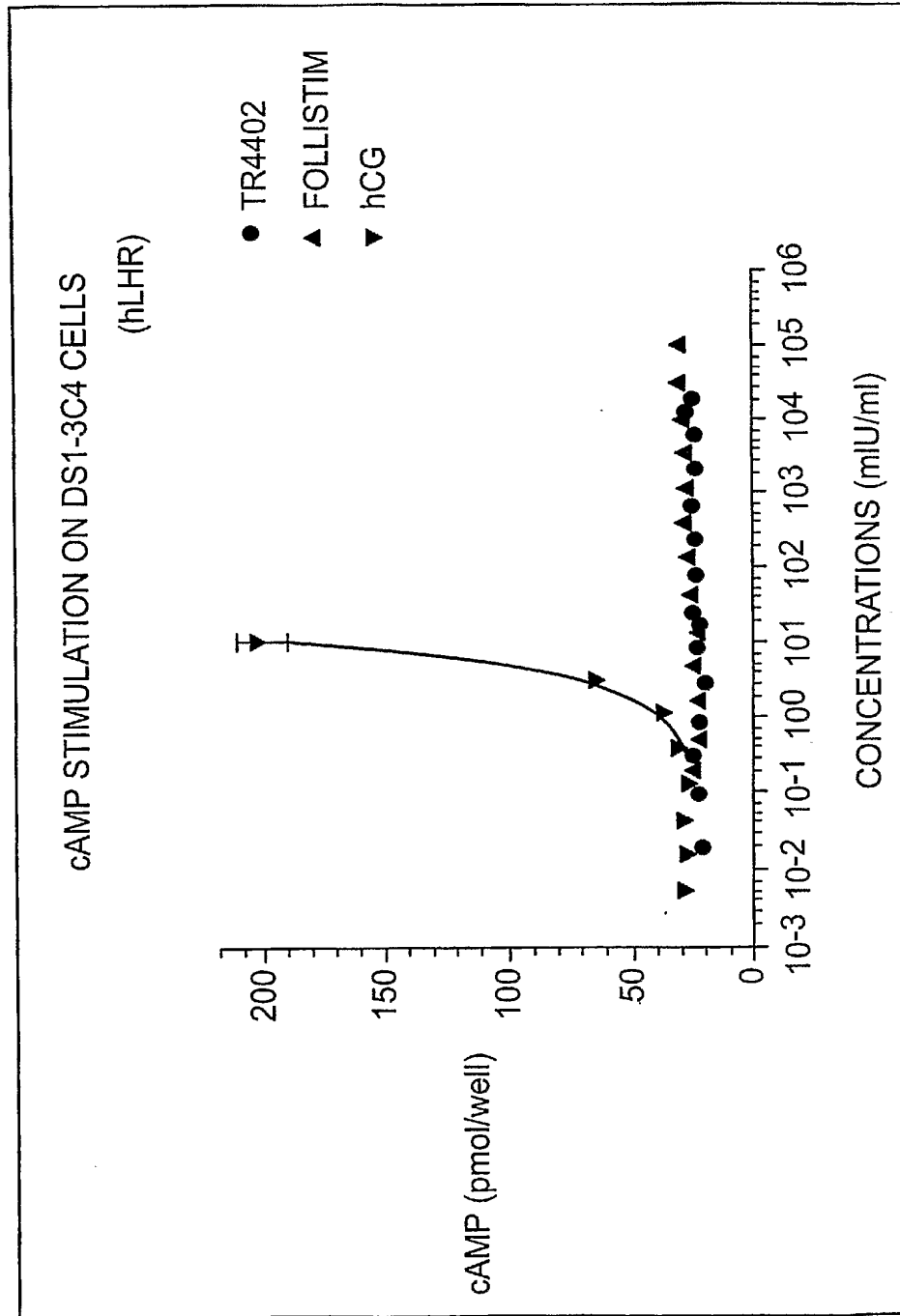
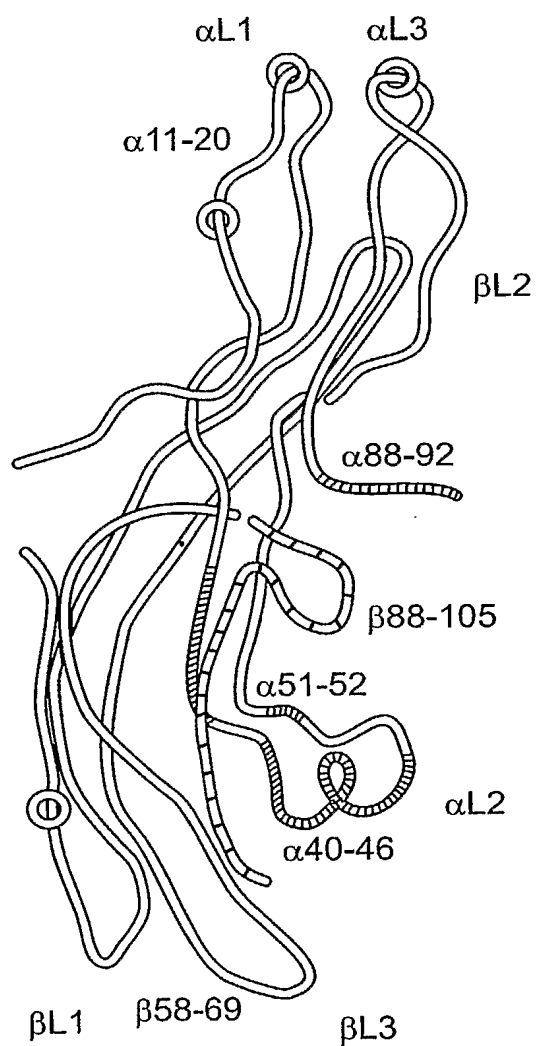


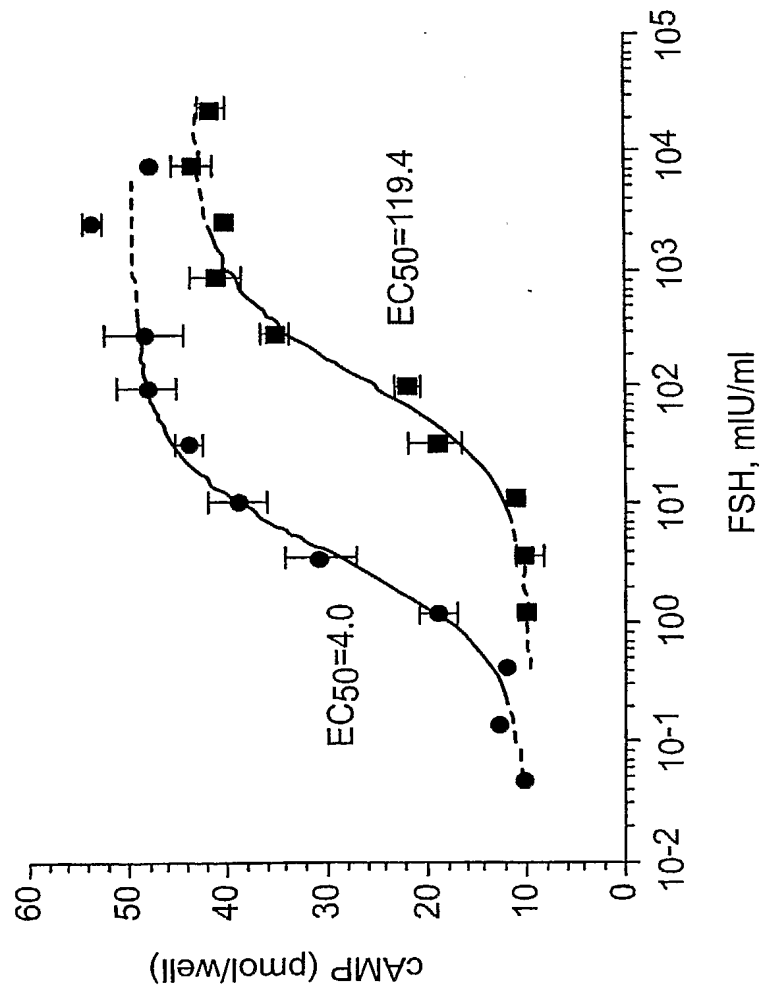
FIG. 4B

11/37

**FIG. 5**

12/37

cAMP STIMULATION ON CHO-FSHR



30X HIGHER POTENCY
17% HIGHER V_{MAX}

● TR4402 LOT2

■ FOLLISTIM DIALYZED

FIG. 6A

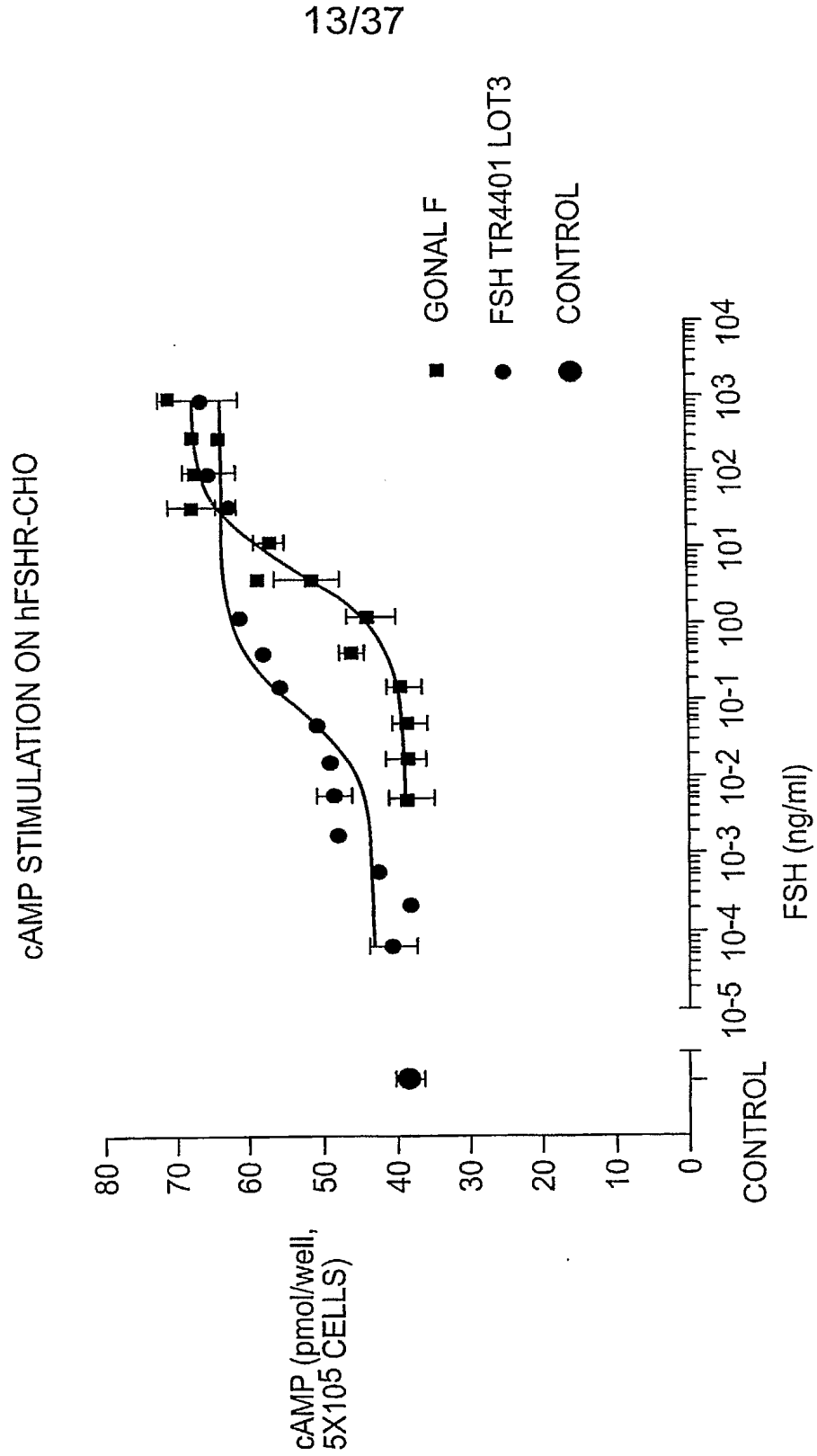
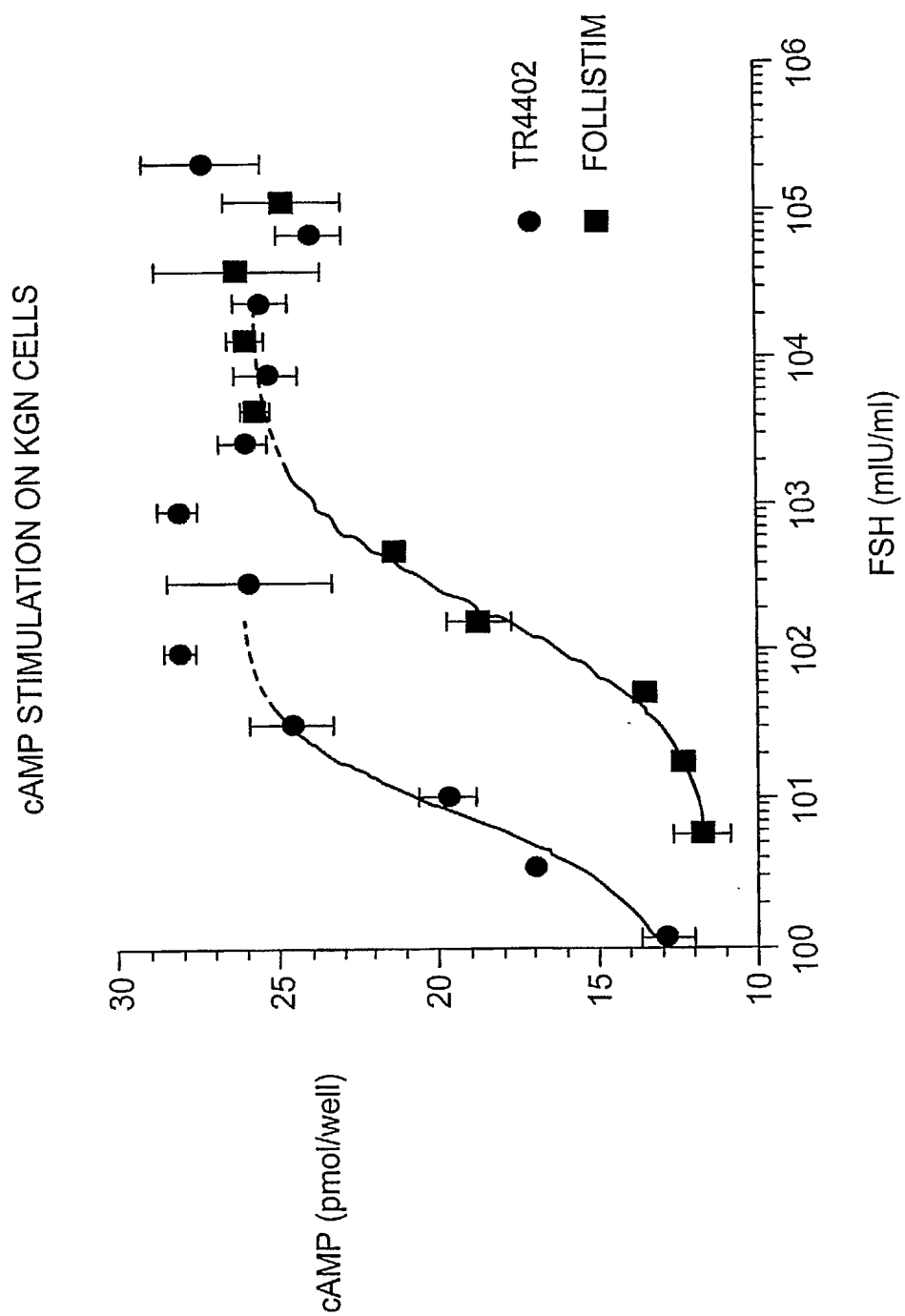


FIG. 6B

14/37

**FIG. 7**

15/37

GLHR-15 CELLS WITH LOW FSHR NUMBER

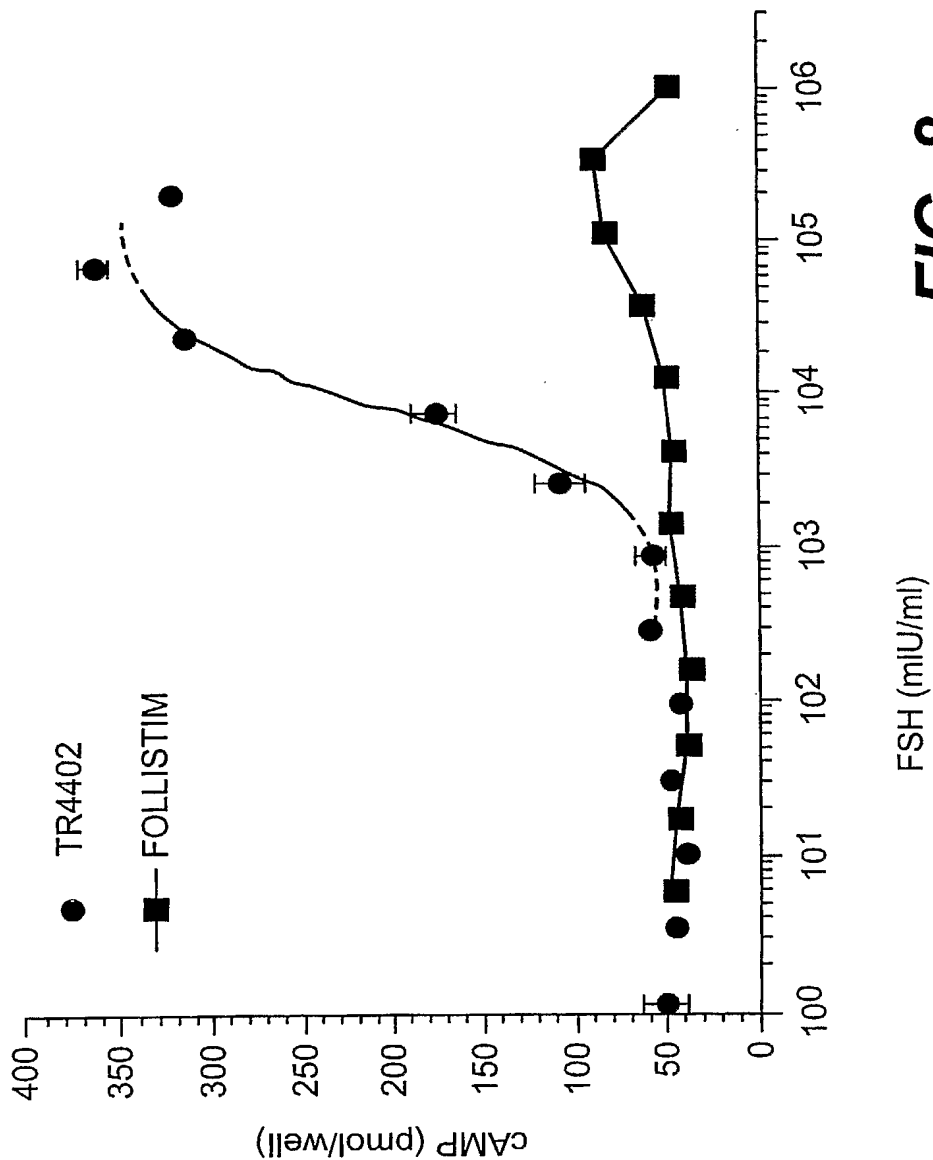


FIG. 8

16/37

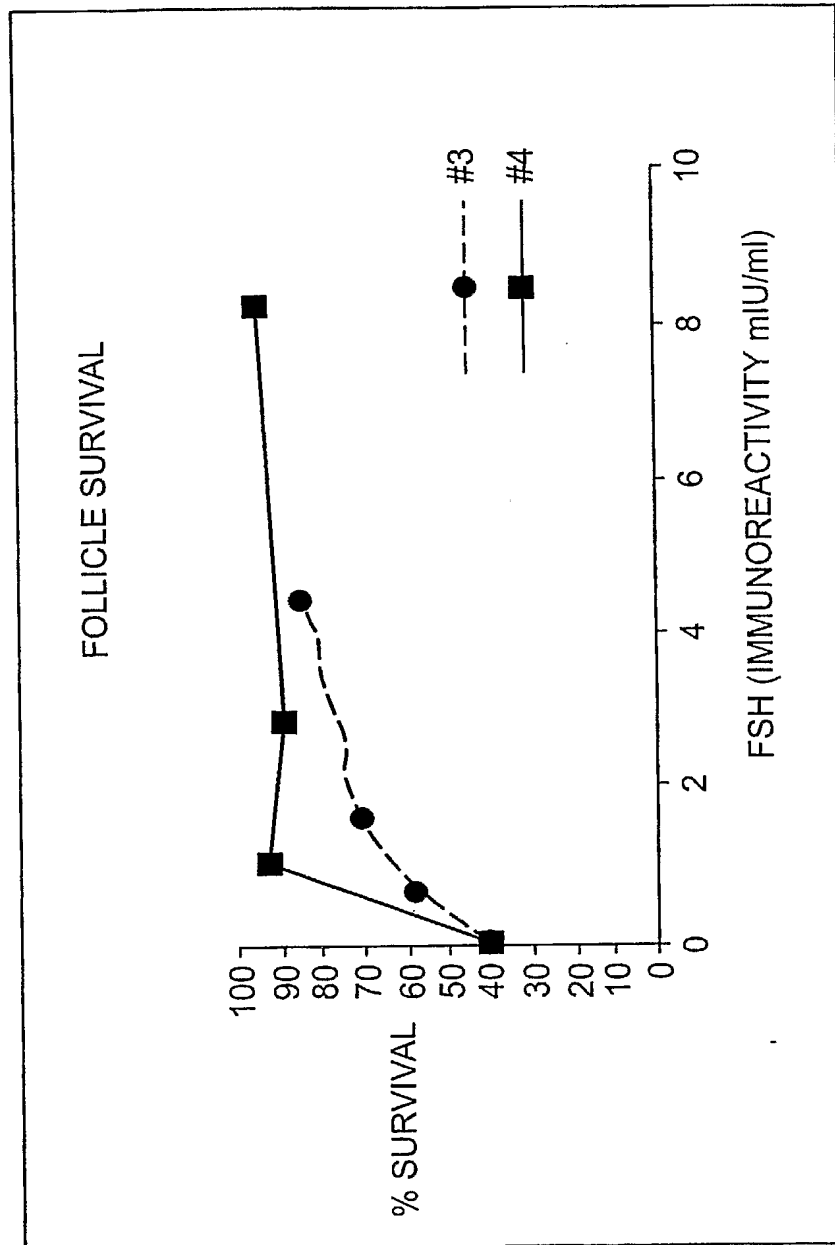


FIG. 9

17/37

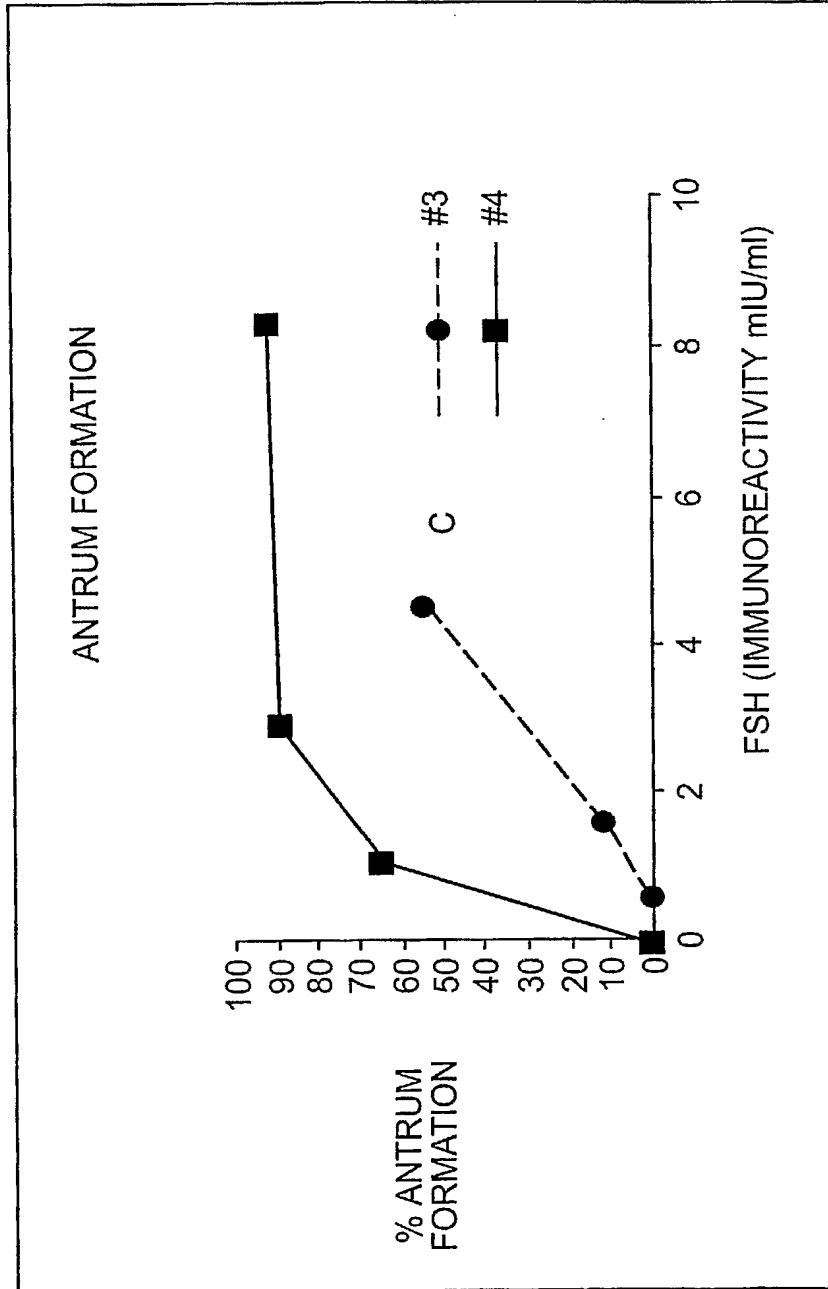
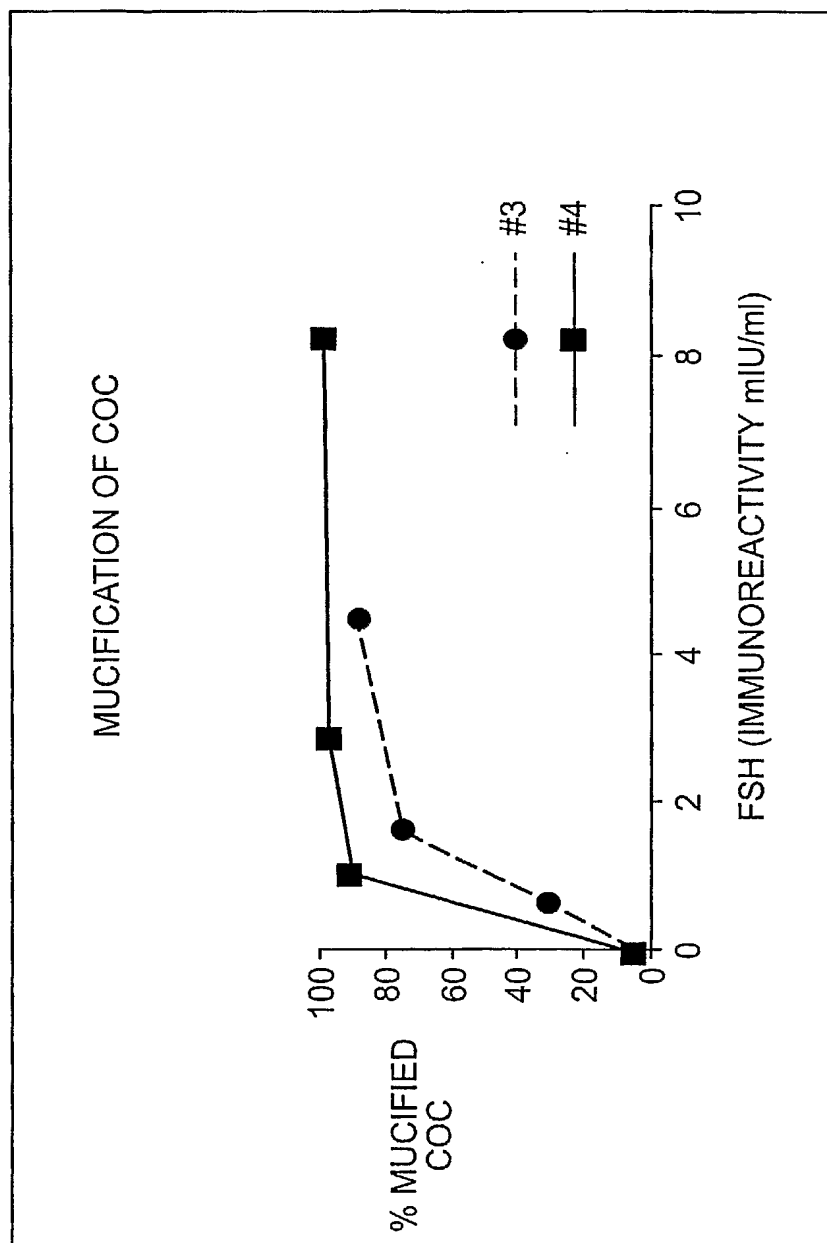
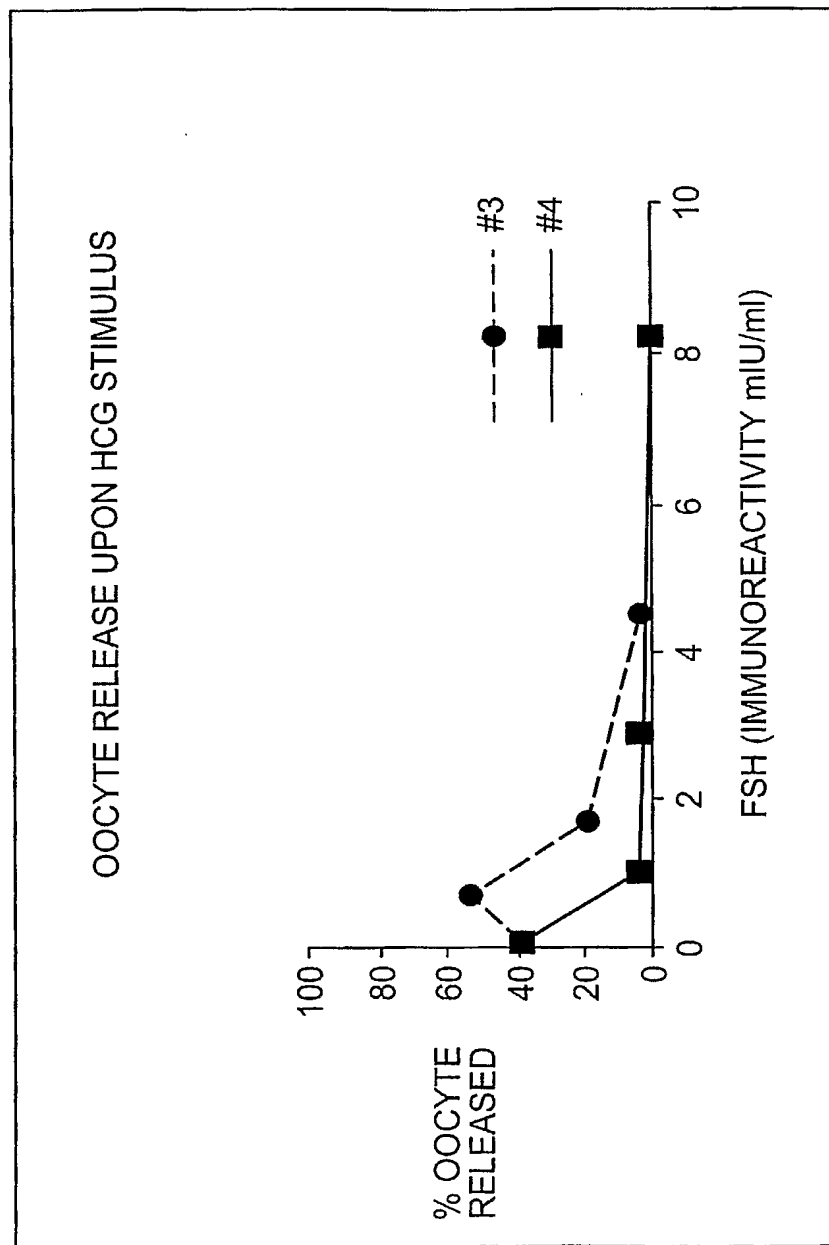


FIG. 10

18/37

**FIG. 11A**

19/37

**FIG. 11B**

20/37

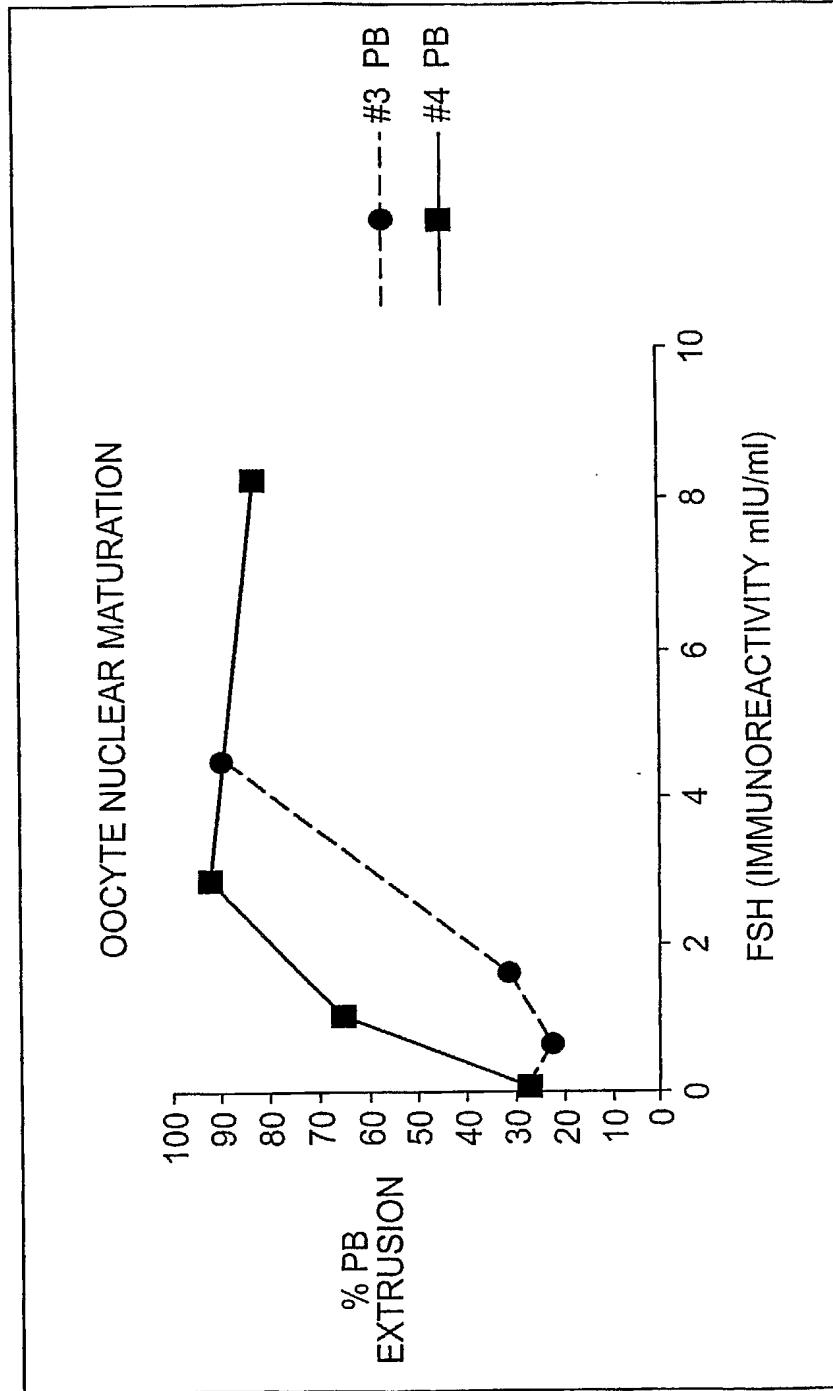


FIG. 12

PROGESTERONE PRODUCTION BY COMPOUND 3

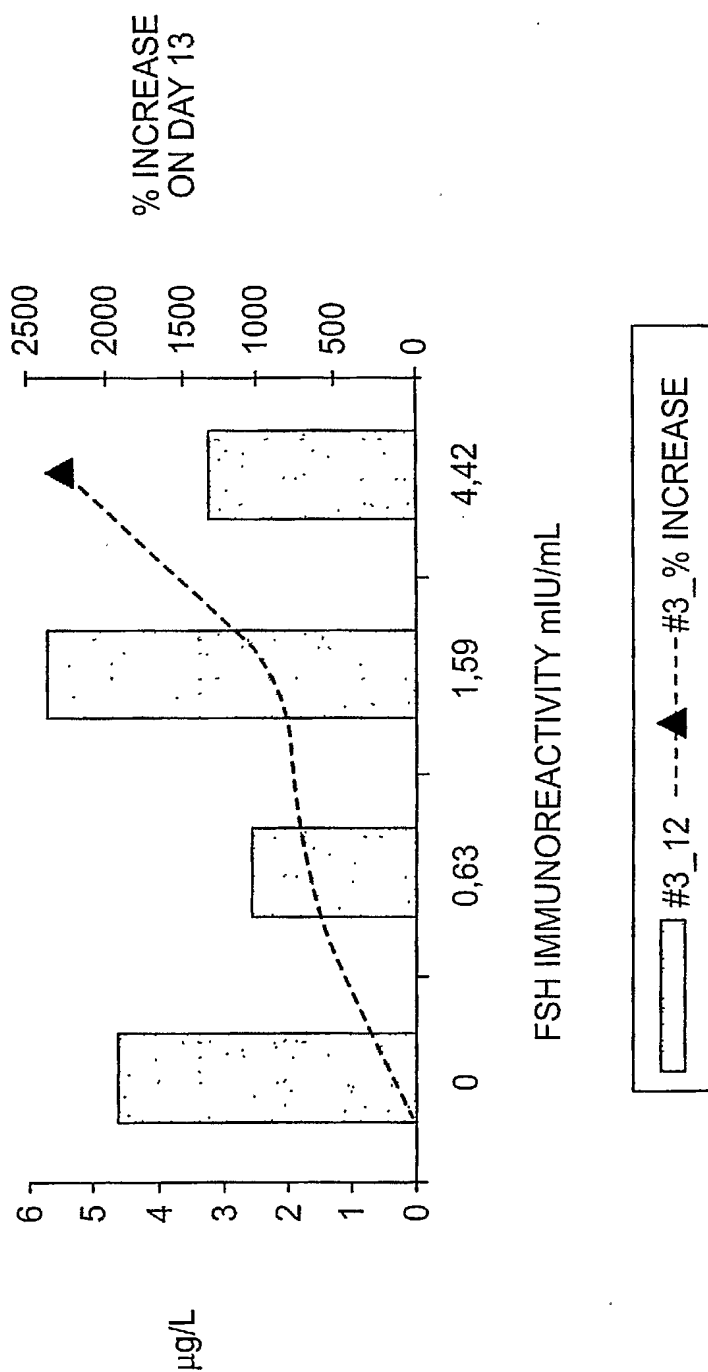


FIG. 13A

22/37

PROGESTERONE PRODUCTION BY COMPOUND 4

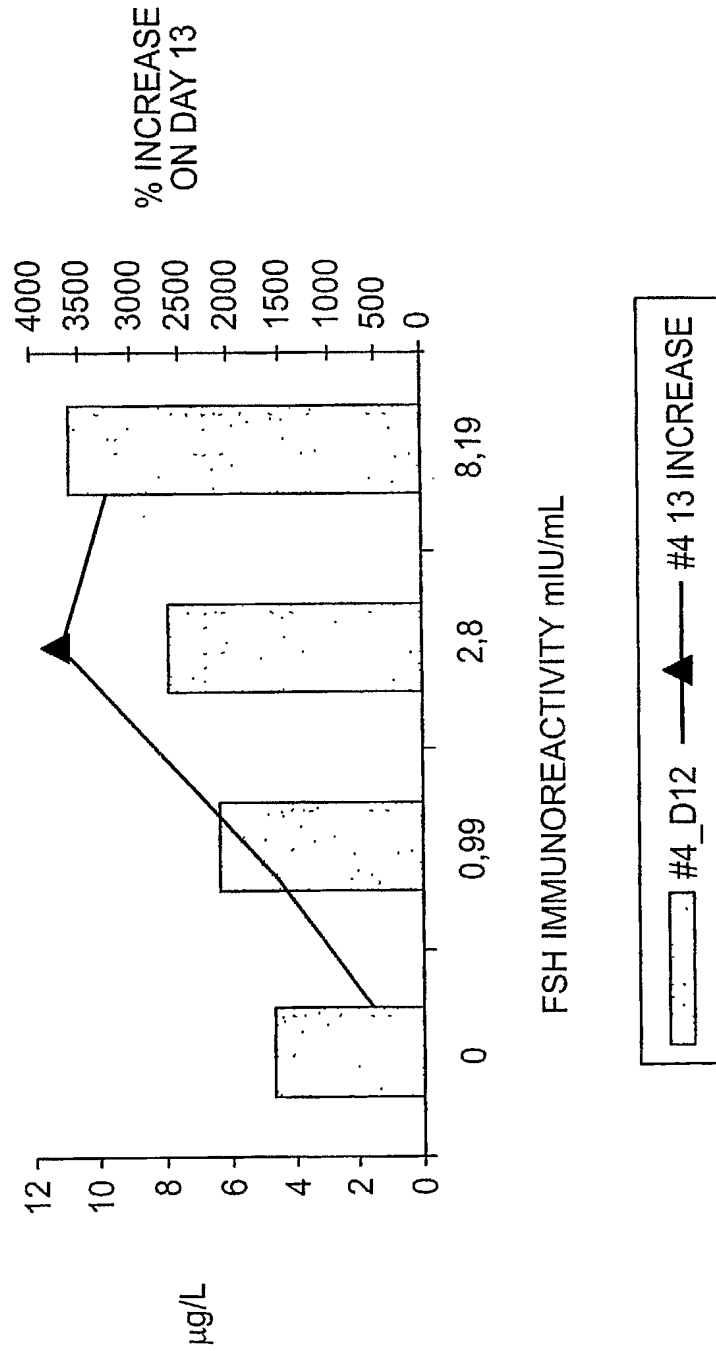
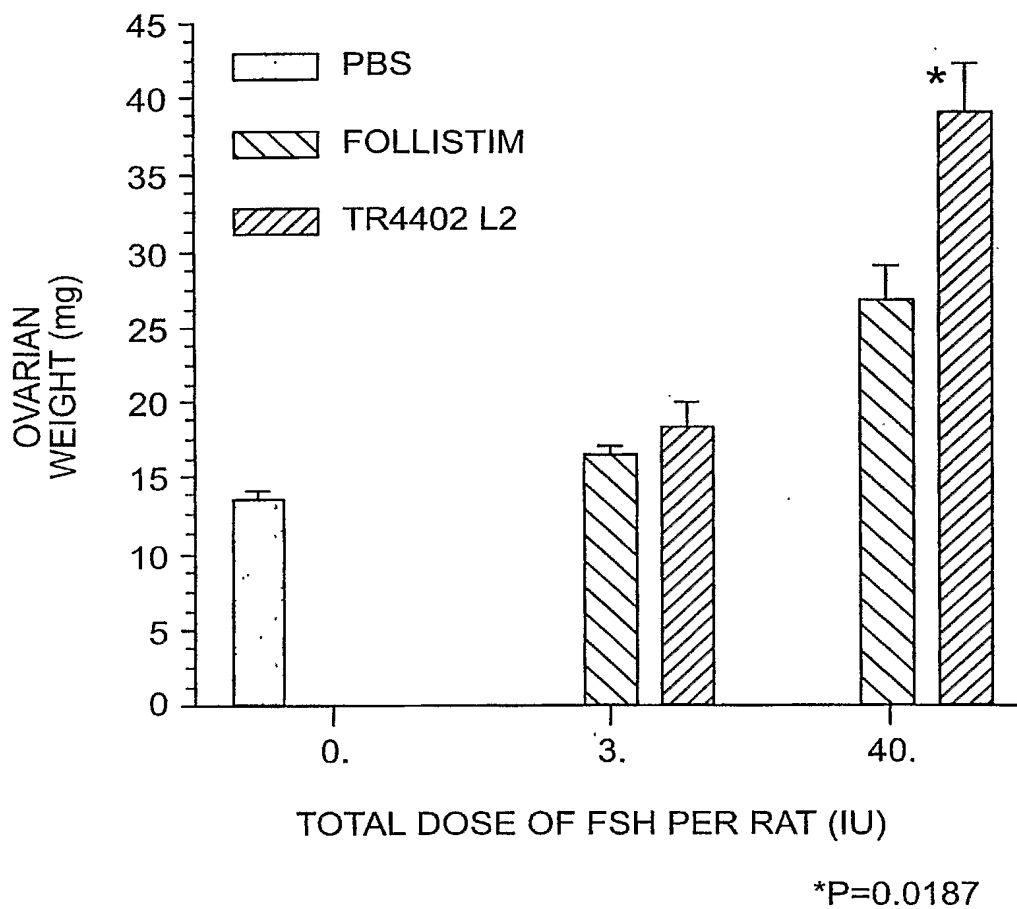


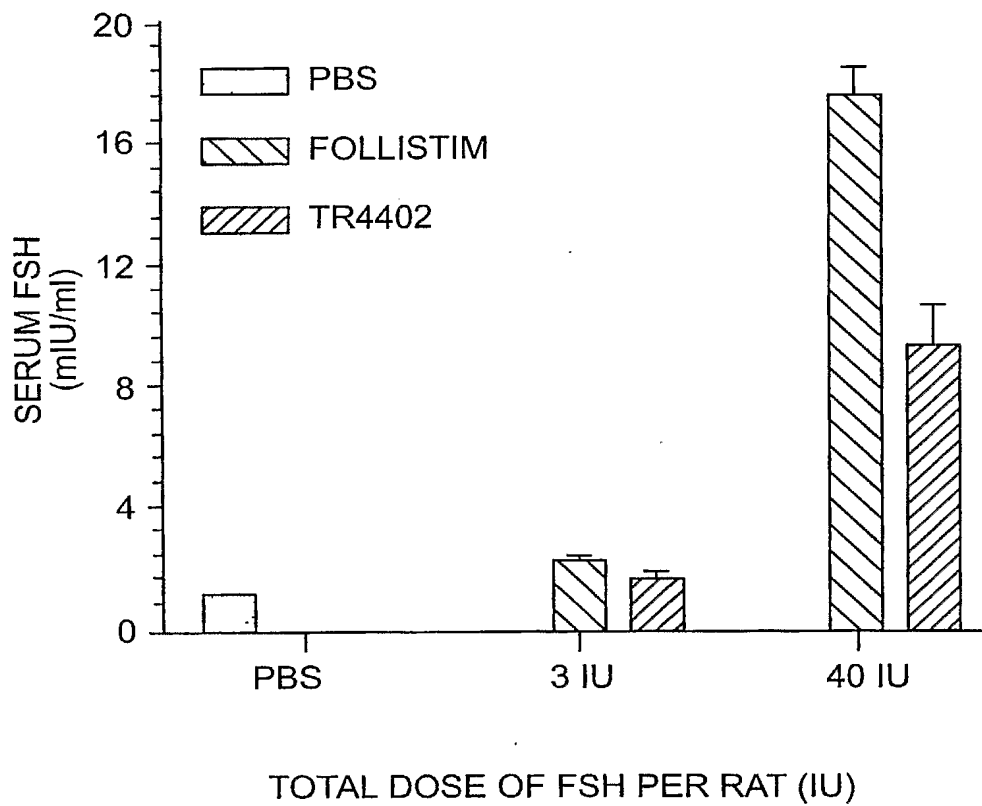
FIG. 13B

23/37

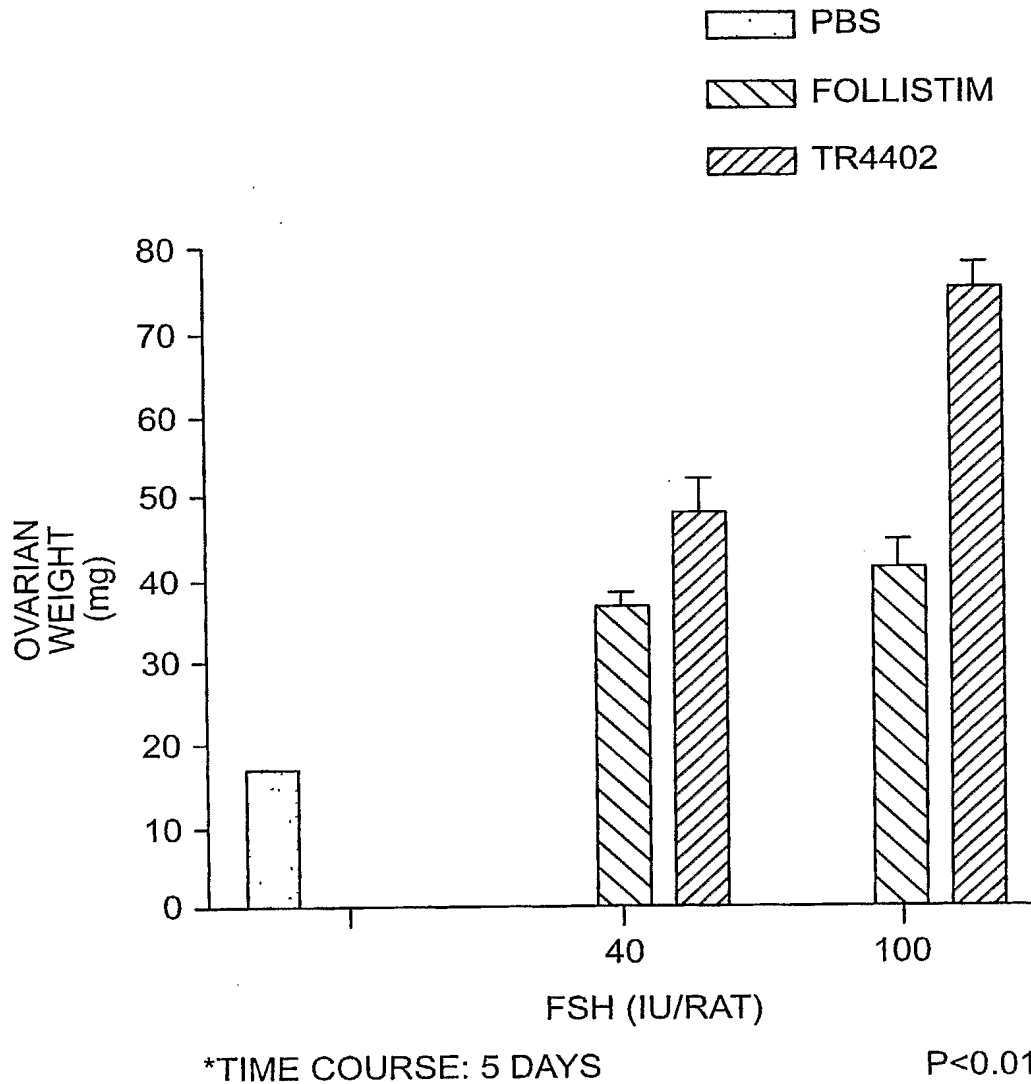
STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS**FIG. 14A**

24/37

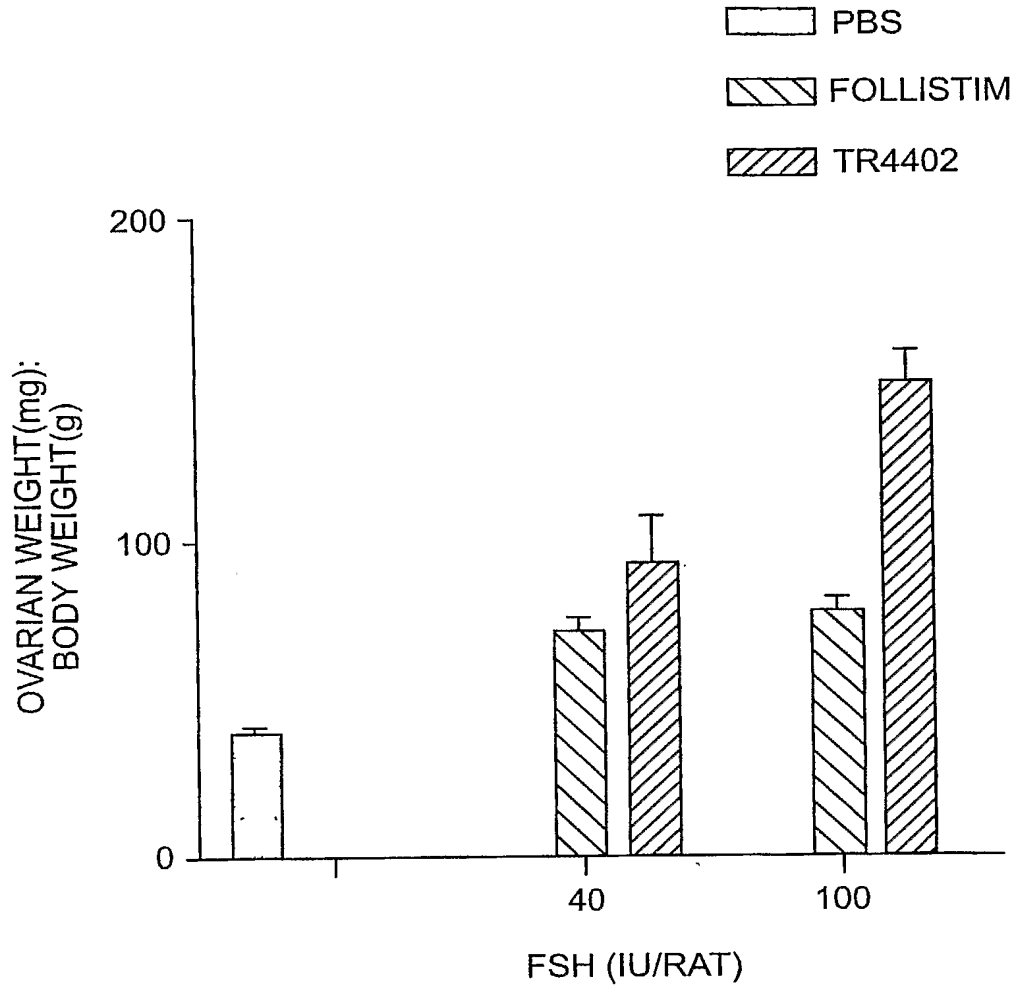
STEELMAN-POHLEY BIOASSAY WITHOUT hVG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS
SERUM FSH LEVELS

**FIG. 14B**

25/37

STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS**FIG. 14C**

26/37

STEELMAN-POHLEY BIOASSAY WITHOUT hCG AUGMENTATION
IN IMMATURE SPRAGUE-DAWLEY FEMALE RATS

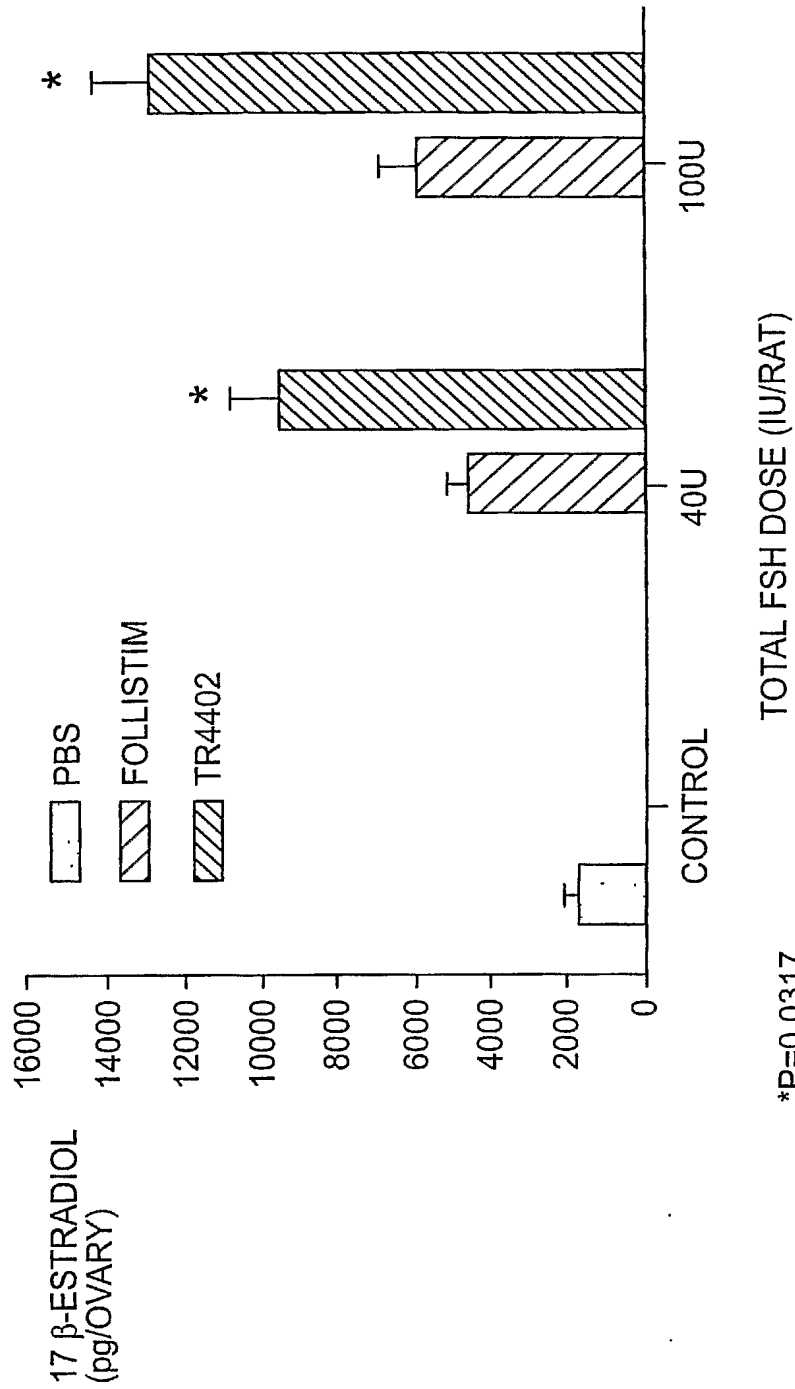
*CORRECTION OF OVARIAN WEIGHT BY BODY WEIGHT
CALCULATED BY: $100 \times \frac{\text{OVARIAN WEIGHT (mg)}}{\text{BODY WEIGHT (g)}}$

*TIME COURSE: 5 DAYS

FIG. 14D

27/37

INTRAOVARIAN 17 β -ESTRADIOL FROM STEELMAN-POHLEY ASSAY



OVARIES WERE COLLECTED ON THE 4TH DAY AFTER THREE INJECTIONS.

FIG. 15

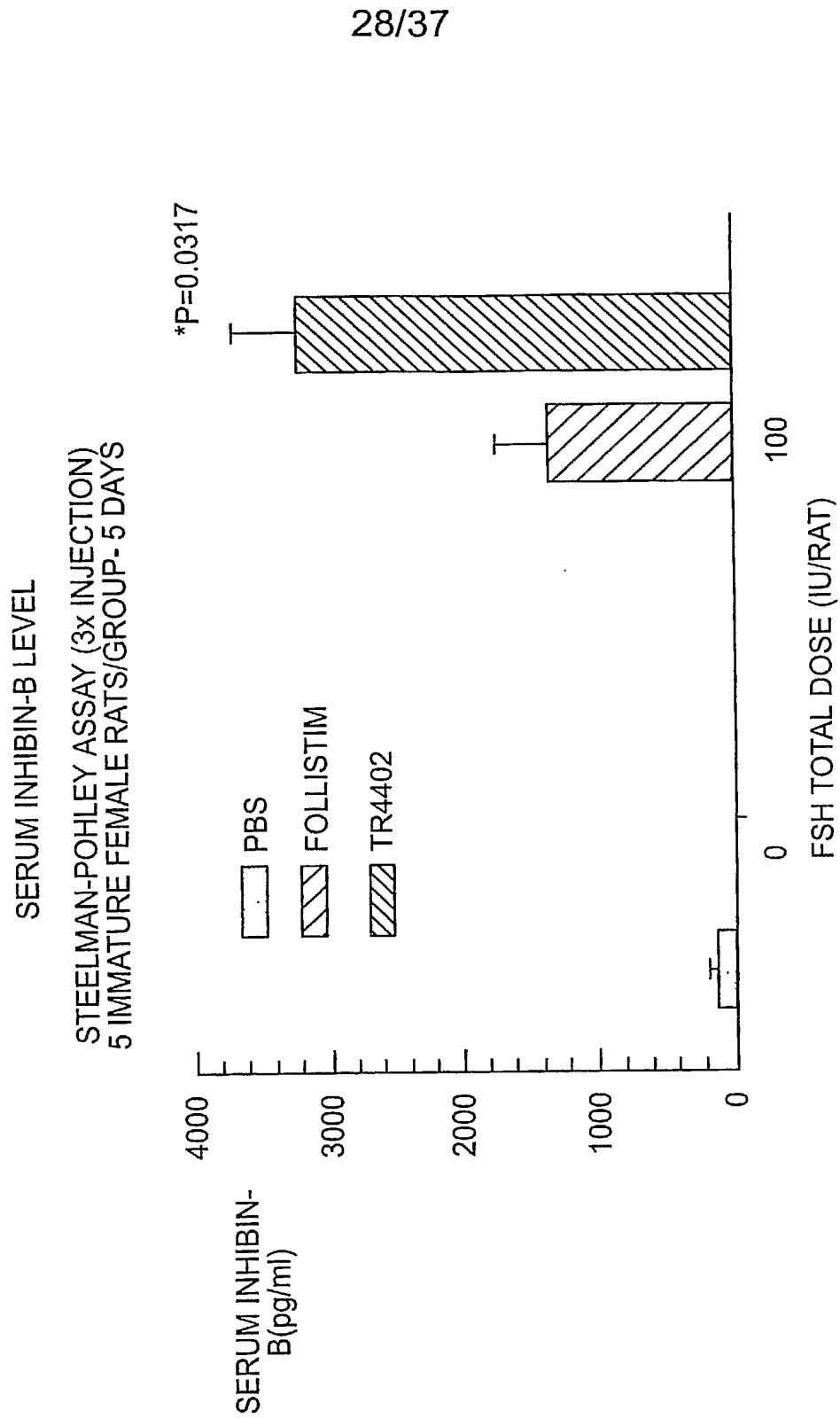


FIG. 16

29/37

FSH CLEARANCE ASSAY

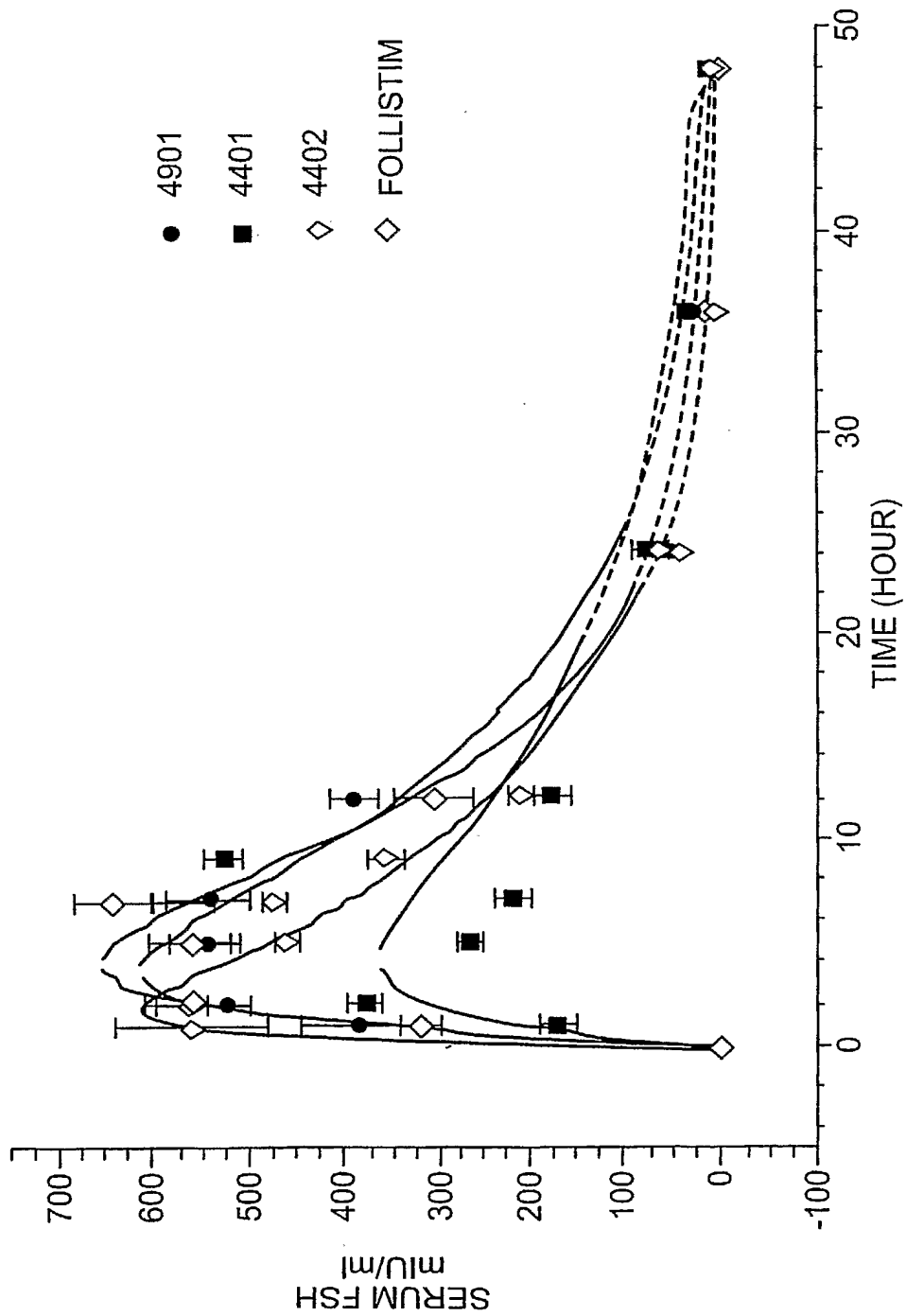


FIG. 17A

30/37

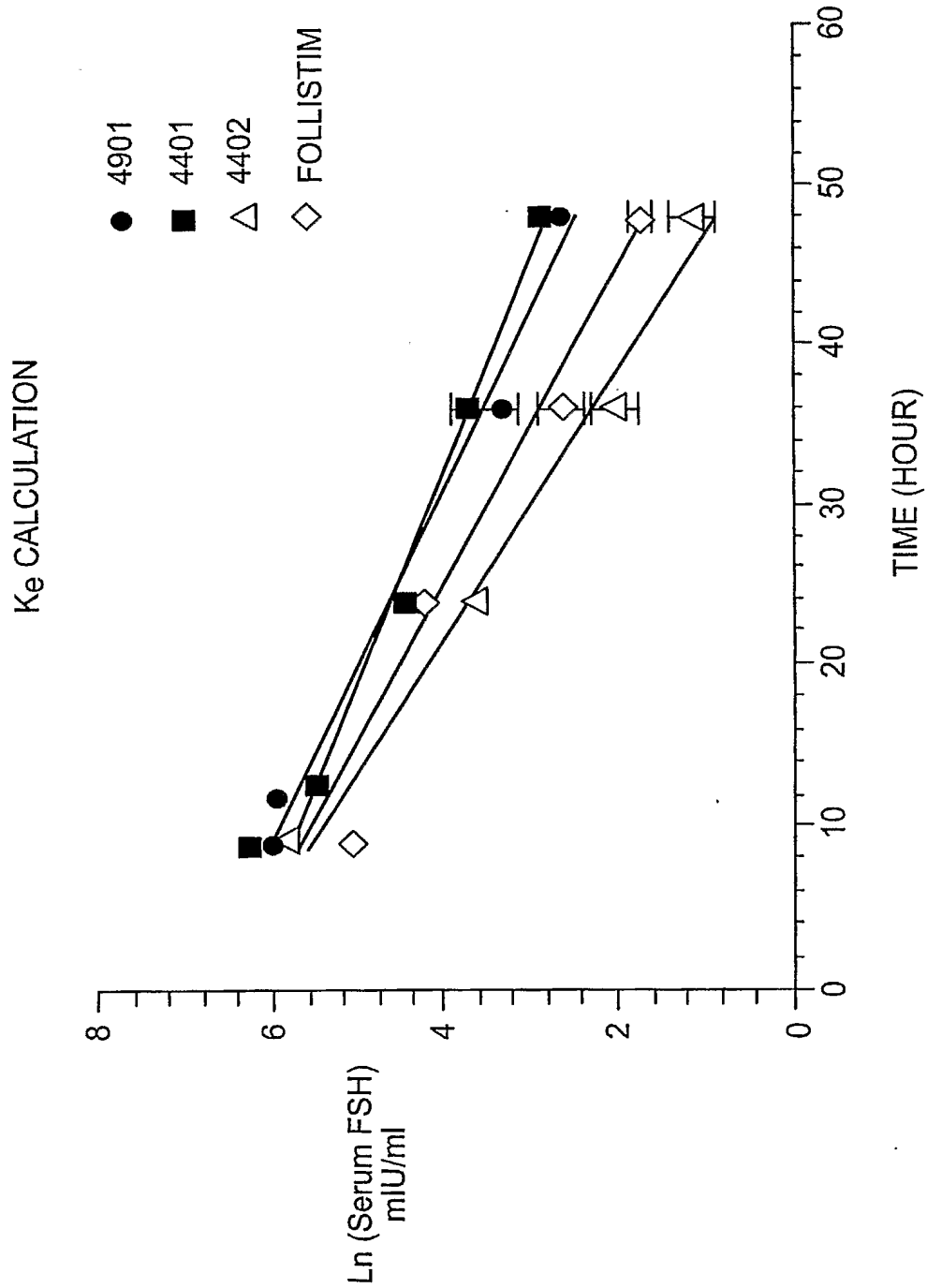


FIG. 17B

31/37

LONGER ACTING TR4402-LA - MODIFIED, NOT BACK TO SCREENING

#1 N-TERMINAL EXTENSION (ANITV)

ANITVApdvqd cpeclqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqkntse stccvaksyn
rvtvmggfkv enhtachcst cyyhks

#2 N-TERMINAL EXTENSION (ANITV) +E14R+Q20R+G73R+βE4R

ANITVApdvqd cpeclqRnp ffsRpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmgRfkv enhtachcst cyyhks

#3 N-TERMINAL EXTENSION (ANITVNITV)

ANITVNITVApdvqd cpeclqenp ffsqpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmggfkv enhtachcst cyyhks

#4 N-TERMINAL EXTENSION (ANITVNITV) +E14R+Q20R+G73R+βE4R

ANITVNITVApdvqd cpeclqRnp ffsRpgapil qcmgccfsra yptplrskkt mlvqkntse
stccvaksyn rvtvmgRfkv enhtachcst cyyhks

#5 V78N

ns cEltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvyetvr vpgcahhads
lytypNatqc hcgkcdsdst dctvrglgps ycsfgemke

#6 E4R + V78N

ns cRltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvyetvr vpgcahhads
lytypNatqc hcgkcdsdst dctvrglgps ycsfgemke

#7 Y58N

ns cEltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypVatqc hcgkcdsdst dctvrglgps ycsfgemke

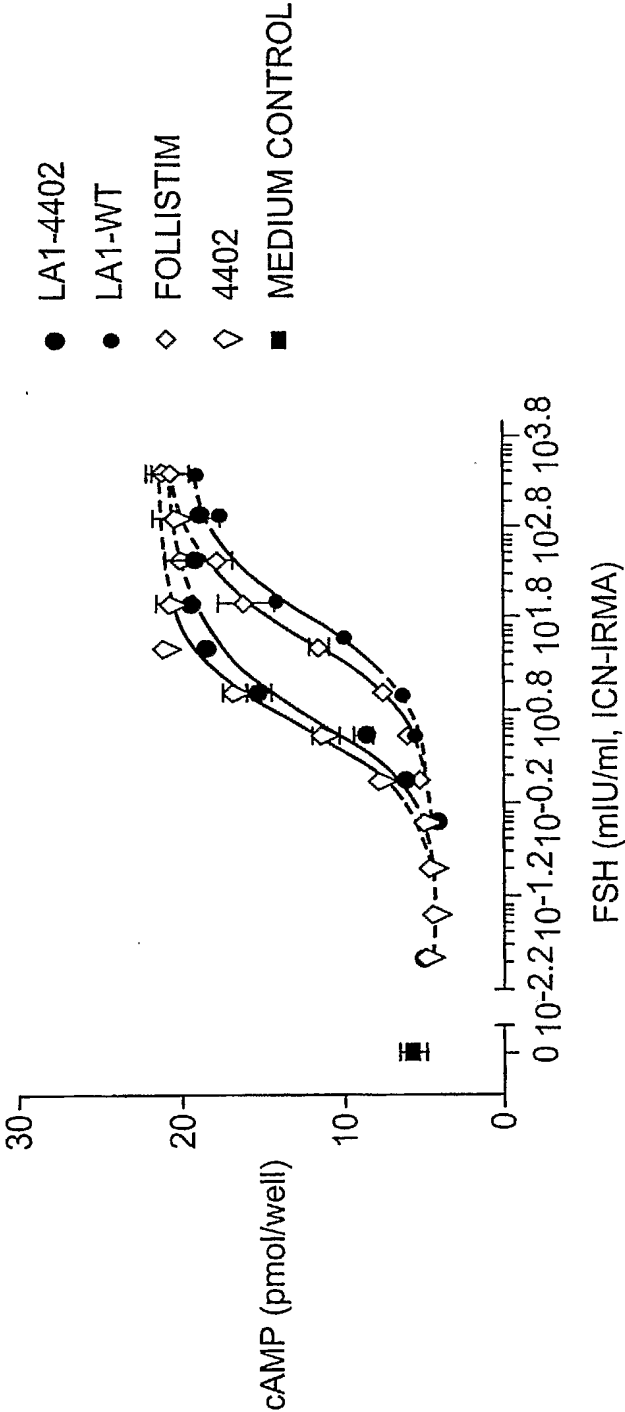
#8 E4R) + Y58N

ns cRltnitiai ekeecrfcis inttwcagyc ytrdlvykdp arpkiqktct fkelvNetvr vpgcahhads
lytypVatqc hcgkcdsdst dctvrglgps ycsfgemke

FIG. 18

32/37

cAMP STIMULATION ON hFSHR-CHO BY LA1-4402 & LA1-wt



	LA1-4402	LA1-WT	FOLLISTIM	4402
EC50	5.939	65.81	41.14	4.324

FIG. 19

33/37

FSH GROUP FOLLOW-UP (PROOF OF CONCEPT)
4402-LA1 ANALOG WITH CORRECTED CLEARANCE OUT-
PERFORMS FOLLISTIM AT ALL DOSES
IN A GROUP OF "POOR RESPONDING" HYBRID MICE

OVULATION ASSAY IN IMMATURE HYBRID B6D2F1 MICE GENE LOGIC 1315-120

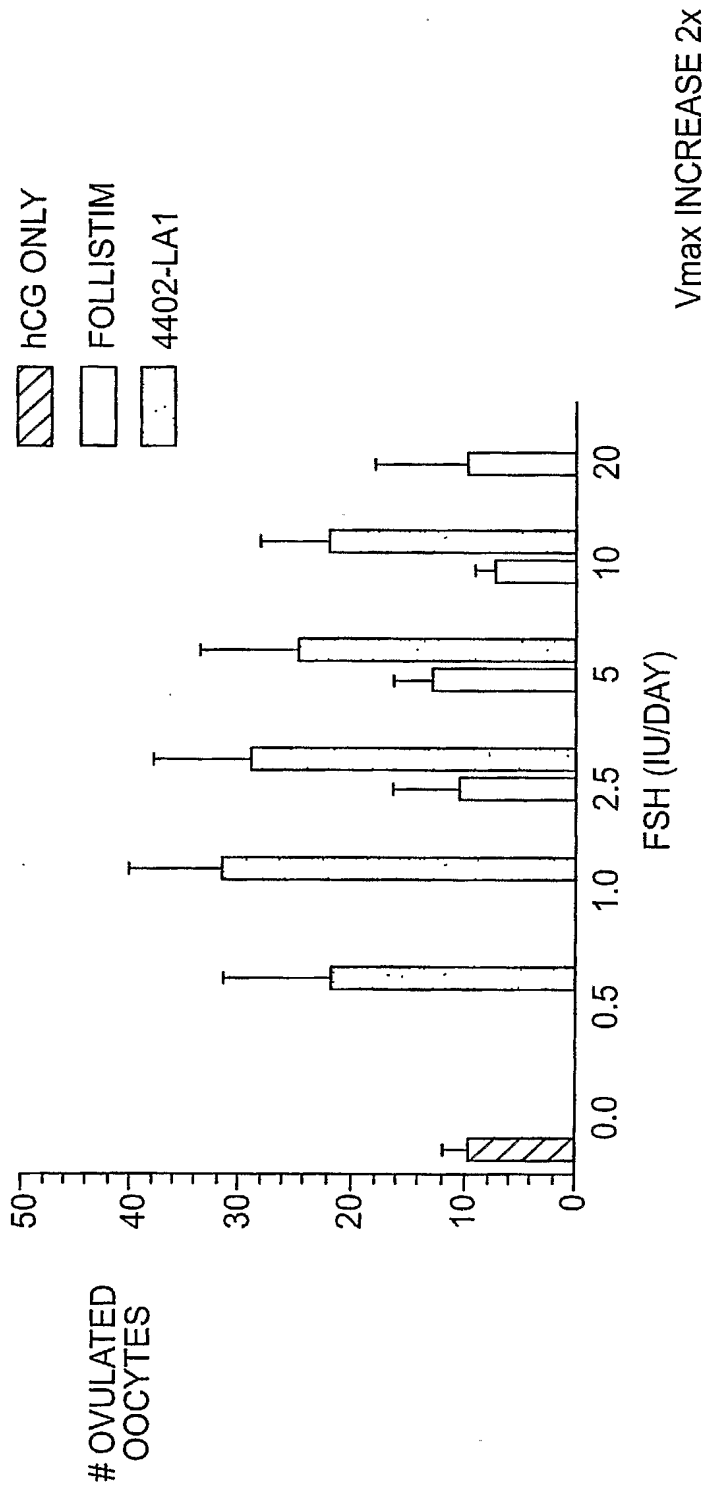


FIG. 20

34/37

TOTAL NUMBER OF HEALTHY OOCYTES (FROM 3 MICE)
COUNTED AT SPERM WASHING

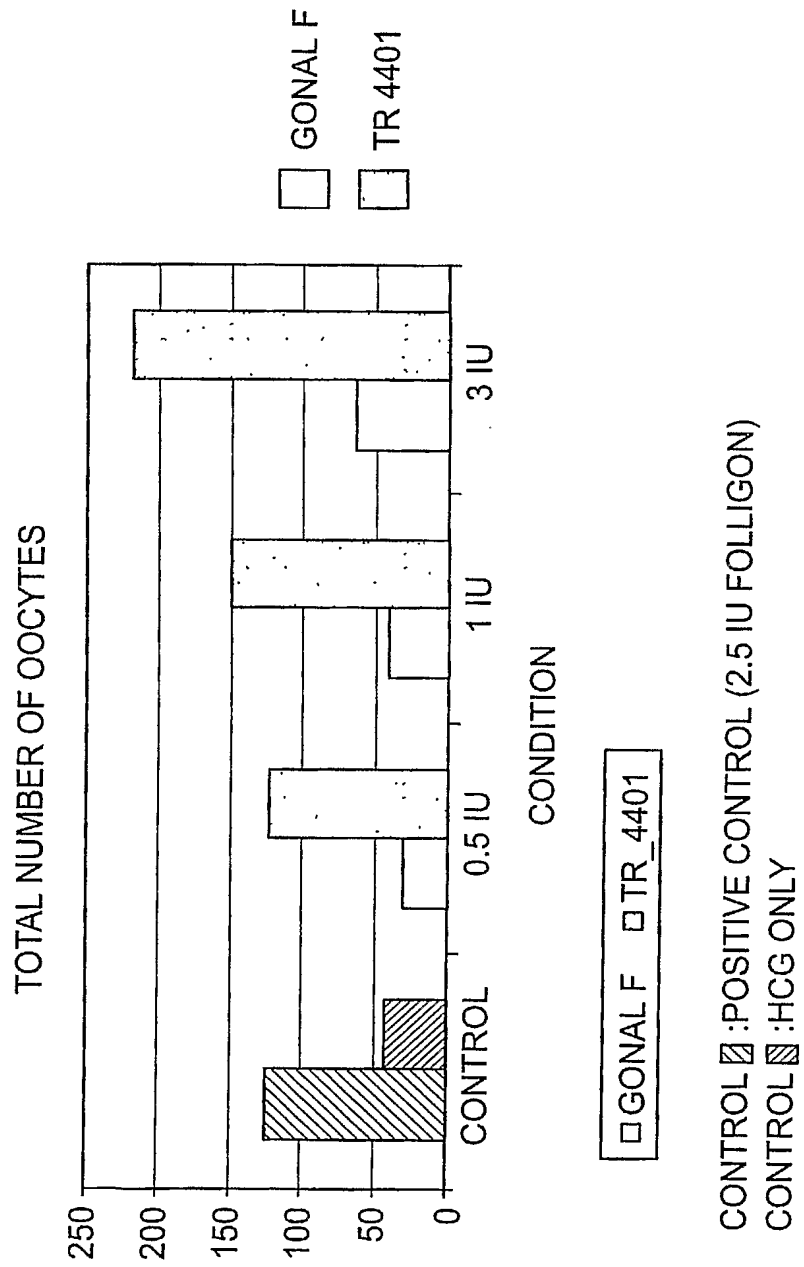
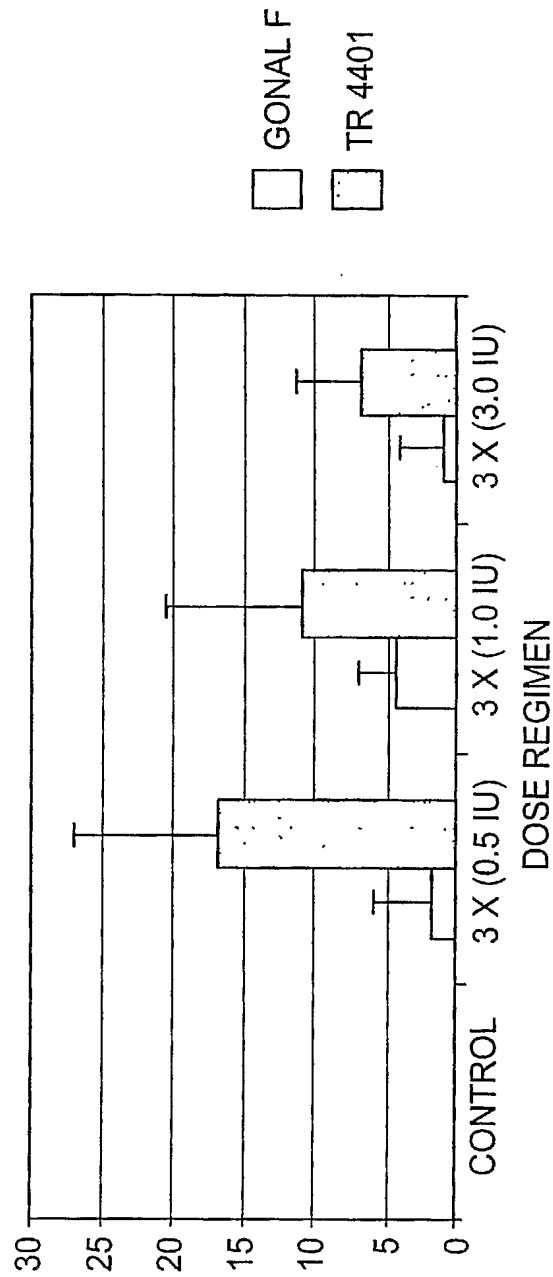


FIG. 21

35/37

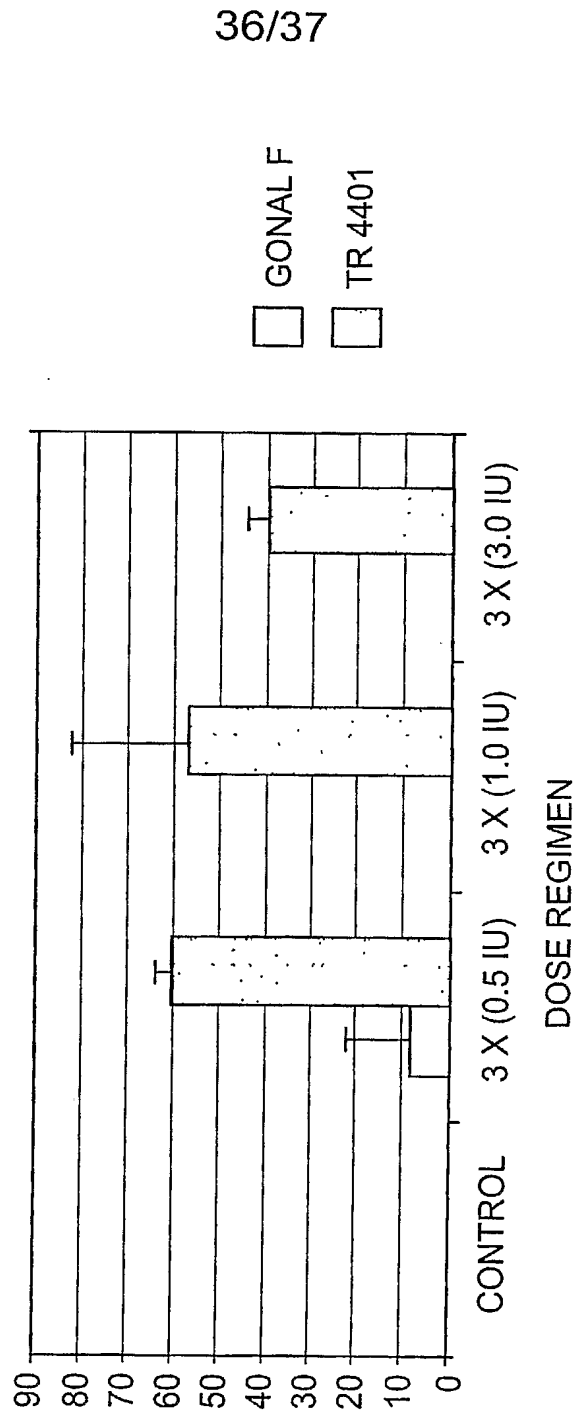
FERTILIZATION RATE EXPRESSED AS % OF 2-CELL/MOUSE



CONTROL: 3 X (1 IU hCG)
 GONAL F AND TR 4401: 3 X (0.5, 1.0, 3 IU COMBINED WITH 1 IU hCG)
 FOLLOWED ON DAY 3 BY 1 OVULATORY DOSE OF 15 IU hCG.

FIG. 22

BLASTOCYST FORMATION RATE EXPRESSED AS % OF BLASTOCYST / 2-CELL



CONTROL: 3 X (1 IU hCG)
 GONAL F AND TR 4401: 3 X (0.5, 1.0, 3 IU COMBINED WITH 1 IU hCG)
 FOLLOWED ON DAY 3 BY 1 OVULATORY DOSE OF 15 IU hCG.

FIG. 23

37/37

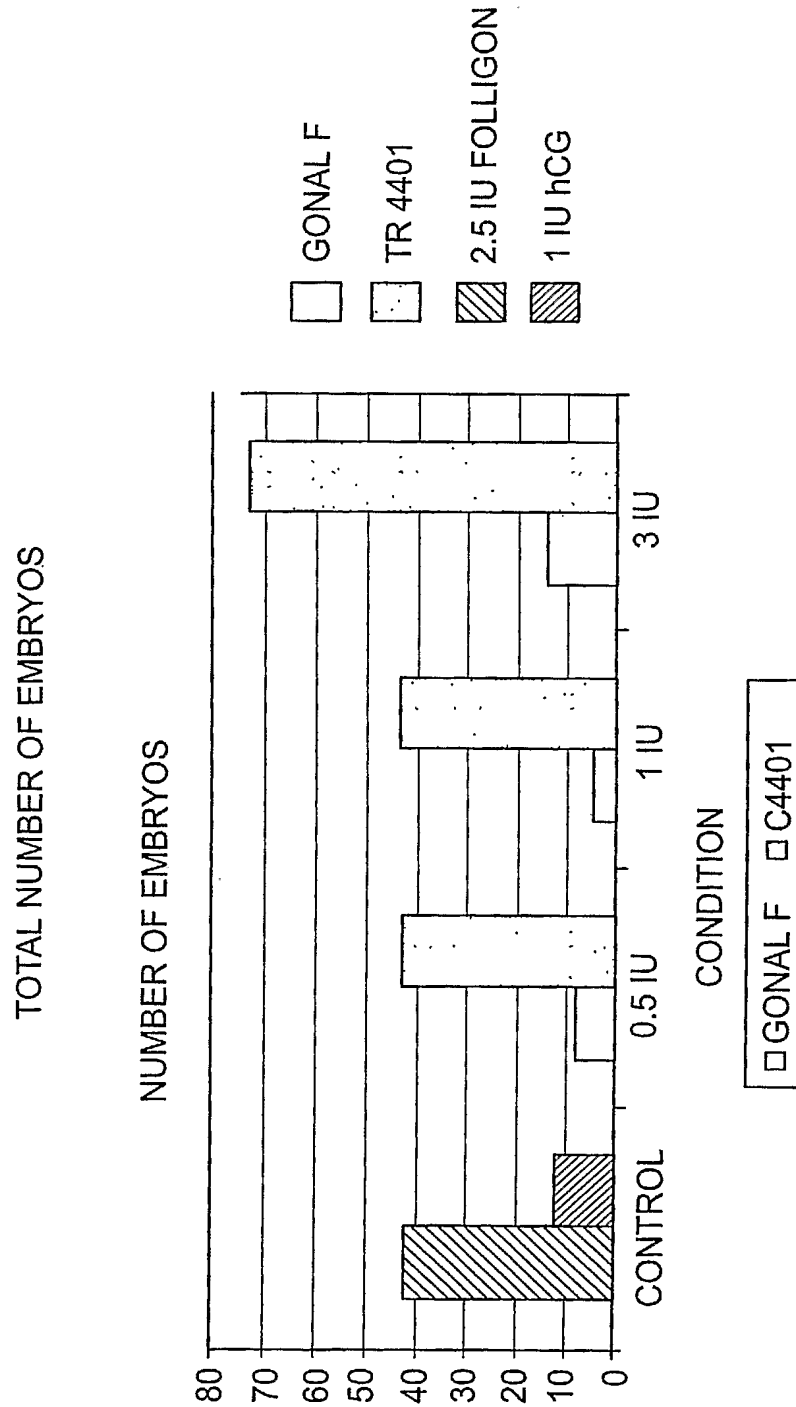


FIG. 24